



Supplement to

**Blood Cell Therapy**  
The official journal of APBMT

# **ABSTRACTS**

**from**  
**the 24th Annual Congress of**  
**APBMT**

**August 30 – September 1, 2019**  
**Busan, Korea**

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# Presidential Symposium



# GvHD Prophylaxis with Post Cy after Haplo-Identical, Matched Unrelated and HLA -Identical Sibling Transplantation

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Allogeneic hematopoietic stem cell transplantation with human leukocyte antigen (HLA)-identical sibling or unrelated donor is a curative treatment option for several hematological malignancies. More recently also haplo-identical stem cell transplantation is increasingly used worldwide since other than T-cell depleting methods to prevent Graft-versus Host Disease (GvHD) have been explored successfully. These, so called T cell repleting strategies are based either on Anti-Thymocyte Globulin (ATG) and Anti-T lymphocyte Globulin (ATLG) or on cyclophosphamide given posttransplant.

Especially the application of post-transplantation cyclophosphamide (post-CY) as a cheap and easy-to-use alkylating agent, has been found to successfully control the intense alloreactive reactions seen after haplo-identical stem cell transplantation. Using the novel post-CY approach pioneered at Johns Hopkins University, haplo-identical transplantations have been remarkably effective in preventing acute and chronic Graft-versus Host disease (GvHD). Thus several groups are now using post Cy also a GvHD prophylaxis also in matched related, matched and mismatched unrelated stem cell transplantation

Post-CY is given usually at 50 mg/kg/day on days +3 and +4d is used alone or in combination with calcineurin inhibitors or /and Mycophenolat Mofetil depending on the characteristics, including donor type. Regardless of the platform, post-CY is historically known to prevent both severe acute and chronic GVHD, to minimize the need for other immunosuppression, and to preserve infectious immunity. Ultimately, this may result in low rates of non-relapse mortality (NRM). A more recent metaanalysis comparing Haplo post CY with MUD,MMUD and HLA identical sibling showed a significantly lower rates of NRM after Haplo identical transplantation and post-CY in comparison with unrelated donors while non-relapse mortality was higher compared with HLA-identical sibling transplantation (MRD). While overall survival was in favor for MRD, no difference in OS between MUD and Haplo-post Cy could be seen , but a OS benefit for Haplo Post Cy in comparison to MMUD. Recent findings suggest that alloreactive T cells are not eliminated after post-CY-based murine transplantation regardless of dose or degree of HLA-matching. CD4+ and CD8+ alloreactive T cells, restrained by regulatory T cells, became functionally impaired in terms of their ability to cause GVHD. In the above mentioned meta-analysis, chronic GVHD and acute GVHD grades 3+4 were significantly reduced by Haplo and post-CY, with a smaller effect in acute GVHD grades 2-4. This finding is in line with previous reports identifying that acute GVHD grade 2 frequently occurs after post-CY and even may be associated with better

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malignancy control.

Overall post Cy as GvHD prophylaxis has become an attractive option also in the non Haplo-setting, but prospective trials are warranted to further investigate the role of post CY in comparison to other GvHD prophylactic approaches

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# Future Changes in Stem Cell Transplantation and Cellular Therapy: Safer, Less Toxic and Less Costly Approaches

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Transplantation of hematopoietic stem cells has been broadly applied and become remarkably safer over the last 4 to 5 decades. Advances in supportive care with safer conditioning regimens, better antiviral and antifungal diagnostics and therapeutics, plus improvements in GVHD management have all led to increased safety and success of transplantation.

These advances in safety have allowed transplantation to be delivered more broadly. With expanded donor registries and cord blood banks plus the newest advances in partially matched haploidentical transplantation, particularly using post-transplant cyclophosphamide, nearly all have an available allogeneic donor and therefor can potentially benefit from the anti-neoplastic effects of an allograft.

But advances in donor availability, transplant safety and prevention and management of GVHD have not been paralleled with improved anticancer potency of an allograft. Malignant relapse remains the primary cause of failure. Though careful patient selection, better pre-transplant disease control with absence of measurable residual disease(MRD) can identify those best able to benefit. Yet the fundamental transplantation approach has been unchanged for many years.

However, novel augmented cellular therapies, antitumor antibodies, cytokines to stimulate T cell, B cell and natural killer cell (NK) lytic attack on residual tumor post-transplant all offer promise that awaits formal testing and proof. Newer, off-the-shelf products, engineered T cells and other novel interventions may limit risks of relapse and improve outcomes even for those with higher risks of relapse.

Yet another big challenge faces our field—the challenge to bring access, availability and affordability of an allograft to patients across the world. Novel molecular diagnostics, advanced and costly pharmaceuticals, intensive molecular and pharmacokinetic monitoring, transfusion support and multidisciplinary care all require well trained staff, experienced practitioners and institutional commitment to deliver this care safely. To date its application has been limited to sophisticated centers and has been most available to countries and regions with greater resources. While the scientific advance is exciting and enticing, implementation research to bring these new tools, techniques and applications to a broader population is equally difficult and broadly needed. Realizing the promise of transplantation will be to translate the great scientific advances into widely available curative therapy for patients across the world. This will require advanced inter-institutional training, sharing expertise, establishing data management for quality assurance and international collaboration. Bringing these elements together will amplify the benefits of transplantation. This will be the best proof of our success and actualize the greatest benefits for more of our future patients.

# Novel Approaches for Treating and Preventing GvHD

**John F. DiPersio, Peter Ruminiski, Karl Staser, Megh Singh, Kidist Ashami, Linda Eissenberg and JaeBok Choi**

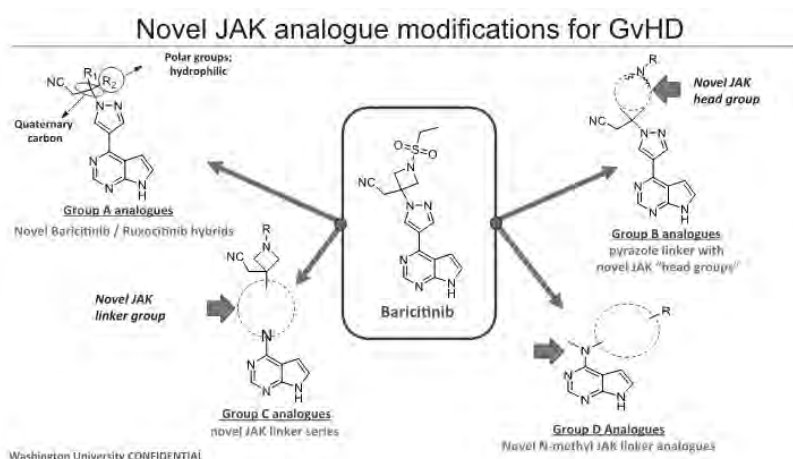
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Graft-versus-host disease (GvHD) is a major and life-threatening complication of allogeneic stem cell transplantation; a treatment which is used to treat and cure multiple types of hematologic malignancies and marrow failure states. There are over 20,000 allogeneic hematopoietic stem cell transplantations (allo-HSCT) performed annually, and approximately 50% will result in GvHD and 50% of those patients will die from complications associated with GvHD. The other 50% of these patients may develop mild, moderate or severe morbidities that can result in life-long debilitation.. The goal of our work is to reduce or eliminate GvHD while maintaining graft vs leukemia (GvL) and improved outcomes for allogeneic stem cell recipients. Additionally, more than 30,000 solid organ transplants are performed in the US alone, of which 25-40% experience episodes of acute and chronic organ rejection. The cumulative cost of treatment and lost productivity in terms of wages runs well into billions of dollars annually. Work by Choi et al (*Blood*, 2012, *PLoS One*, 2014) has implicated gamma interferon receptor signaling in GvHD via modulation of CXCR3 expression and donor T cell trafficking to sites of GvHD/inflammation. Our group has further demonstrated that pharmacologic inhibition of gamma interferon receptor (INF $\gamma$ R) signaling with JAK1/2 balanced (ruxolitinib) and JAK1-specific inhibitors (itacitinib) can both prevent GvHD and treat established GvHD in mice and in man (Schroeder et al ASH, 2016 and Khoury et al BMT, 2018). Here we show that a novel balanced JAK1/2 inhibitor, baricitinib is not only significantly more effective at treating and preventing acute GvHD than all other JAK inhibitors tested (Choi et al Leukemia, 2018) but also completely blocks chronic GvHD in a B10.D2 to BALB preclinical model of chronic GvHD and completely reverses established acute GvHD. Finally baricitinib not only has a potent impact of prolonging MHC mismatched skin graft survival (B6 to BALB) (3 days for cyclosporine vs 15 days for baricitinib) but when added to cyclosporine indefinitely (>200 days) prolonged the rejection of these same MHC mismatched skin grafts.

We have utilized and will present our comprehensive filtering funnel to identify new and structurally novel JAK inhibitors and derivatives of baricitinib that have enhanced physiochemical, PK, PD and in vivo biologic properties compared to the best in class JAK inhibitor, baricitinib and that can potentially advance into human clinical trials. Our comprehensive testing funnel includes rational chemical modification of the parent baricitinib structure, coupled with serum free enzyme assays, human whole blood enzyme assays, PK, PD assays, in vitro inhibition of CXCR3 upregulation in activated T cells in vitro as well as several in vivo assays

including in vivo skin graft survival and in vivo inhibition of GvHD while maintaining GvL

Initial medicinal chemistry (**Figure 1**) efforts toward this objective have identified a novel JAK inhibitor (WU-12) that is first potent pan-JAK inhibitor (IC<sub>50</sub> for JAK1,2,3 and TYK2 all <1-10 nM) and which is more potent than baricitinib in preliminary in vitro enzyme, whole cell enzyme assays and phospho STAT signaling assays. Emerging structure activity relationships (SAR) and on-going drug optimization strategies will be discussed. In addition to our lead candidate we have also synthesized and rationally designed other alternate candidates (WU10, WU13, WU15) with enhanced activity compared to baricitinib but with different JAK1/2/3/TYK2 specificities compared to other JAK inhibitors developed and currently under development by others (**Figure 2**). Our optimal candidate(s) can be validated in both mouse and large animal models of both stem cell and solid organ transplant as their next step toward clinical development.



**Figure 1.** Medicinal Chemistry Design for Novel Baricitinib-like JAK1/2 Inhibitors

	IC <sub>50</sub> nM				Relative to best nM				
	JAK1	JAK2	JAK3	TYK2	JAK1	JAK2	JAK3	TYK2	All
WU12	0.453	0.133	1.14	0.417	100.00%	100.00%	33.77%	100.00%	83.44%
Baricitinib	0.766	0.224	8.81	2.21	59.14%	59.38%	4.37%	18.87%	35.44%
Ruxolitinib	1.04	0.285	7.91	1.53	43.56%	46.67%	4.87%	27.25%	30.59%
PF06651600	300	108	0.385	551	0.15%	0.12%	100.00%	0.08%	25.09%
WU10	1.07	0.535	18.3	2.84	42.34%	24.86%	2.10%	14.68%	21.00%
Tofacitinib	1.82	2.2	0.81	16.8	24.89%	6.05%	47.53%	2.48%	20.24%
BMS911543	424	0.892	214	57.4	0.11%	14.91%	0.18%	0.73%	3.98%
PF04966842	3.24	31.9	704	51.8	13.98%	0.42%	0.05%	0.81%	3.81%
WU15	4.34	8.22	60.8	29.4	10.44%	1.62%	0.83%	1.42%	3.53%
Oclacitinib	5.22	11.9	53.2	31.9	8.68%	1.12%	0.72%	1.31%	2.96%
WU14	77.7	35.1	36.2	578	0.58%	0.38%	1.06%	0.07%	0.52%
WU13	74.2	54.2	418	574	0.61%	0.25%	0.09%	0.07%	0.26%

**Figure 2.** Comparison of IC<sub>50</sub> of Wash U Novel JAK inhibitors to commercially available JAKi



# Design the Future of Hematopoietic Cell Transplantation (HCT) in Asia-Pacific Countries/Regions

**Shinichiro Okamoto**

Keio University School of Medicine, Tokyo, Japan

The first hematopoietic cell transplantation (HCT) was performed 60 years ago. Since then the transplant procedure has been constantly improved by incorporating multiple progress in clinical practice such as better management of infectious complications, introduction of HLA allele typing, the expansion of stem cell donors, and so on. With those progress the number of HCT have continued to increase; however, HCT remains a complex procedure facing a dual challenge: cure of the underlying diseases and prevention of relapse while controlling potentially fatal complications.

At present HCT starts moving from the age of expansion to the age of refinement. Enlightened use of innovative targeted and immunotherapeutic agents or cellular therapies in combination with HCT promises to reduce relapse and further improve HSCT outcome. Contemporary immunotherapies are already being effectively administrated in conjunction with HCT to prevent life-threatening viral infections or relapse of malignant diseases. Limited GVHD with post-transplant high dose cyclophosphamide or other novel approaches makes HCT an attractive platform for the post-transplant use of innovative cellular and immunotherapies in selected patients. However, translation of those promising approach into first-line clinical routine is still limited by the availability of technique, limited compatibility of classical phase III designs with cellular therapy, and more importantly, regulatory restrictions. Multinational efforts and global collaboration of HCT societies are definitely required to overcome the obstacles. In addition, the unique challenge exists in Asia-Pacific countries/regions.

About two third of countries/regions HCT still remains in the age of exploration and expansion in HCT, and those countries varied significantly in terms of the diseases for which transplantation are indicated, the infrastructure for supporting HCT, financial supports and regulatory policies for innovative therapies, and endemic of infectious diseases. Thus the APBMT has to play a crucial role to foster the activity of HCT in each country by providing them with HCT training opportunities, ensuring the quality of HCT, establishing transplant outcome registry, and establish the solid and sustainable platform of HCT. I believe it will lead to additional meaningful progress and further refinement of this life-saving procedure in Asia-Pacific Countries/regions.

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# Plenary Session



# Hematopoietic Stem and Progenitor Cell Genetic Modification to Model Human Diseases and Develop New Therapies

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The rhesus macaque autologous transplantation model has been predictive and instructive in better understanding human hematopoiesis and translating novel gene and cell therapies to the clinic. We have developed a robust CRISPR/Cas9 gene editing platform for hematopoietic stem and progenitor cells (HSPC) in this model. Engraftment of multilineage HSPC with up to 90% of edited knockout alleles has been achieved in macaques. We have created a macaque model of age-related clonal hematopoiesis (ARCH) following autologous transplantation of edited HSPC in macaques, demonstrating reproducible clonal expansion of engrafting HSPC with either TET2, DNMT3A or ASXL1 edited loss-of-function alleles, and gained insights into hematopoietic and cardiovascular manifestations of ARCH. Interventions to accelerate or inhibit clonal expansion are being investigated in this model. We have also utilized editing of the *PIGA* gene to investigate intrinsic versus extrinsic pathways resulting in HSPC clonal expansion in the poorly understood disorder paroxysmal nocturnal hemoglobinuria. Finally, we have pursued knockout of CD33 as an approach to protect normal HSPC from CAR-T attack, providing a pathway to safe and effective utilization of CAR-T in the treatment of myeloid malignancies. In addition, we have compared approaches to predict off-target effects in normal primary engrafting HSPC, investigating whether sites predicted by *in silico* algorithms or by CircleSeq, a method for selective sequencing of DNA exposed to nucleases *in vitro*. Hematopoietic cells containing appreciable levels of off-target editing predicted by CircleSeq have been detected following transplantation of edited HSPC.

# Outcome of Unmanipulated Haploidentical Transplants in Leukemia: An Update on 500 Patients

Andrea Bacigalupo

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**Background:** We have reported the use of two myeloablative regimens, for unmanipulated related haploidentical transplants (HAPLO) with post transplant cyclophosphamide (PT-CY) on 50 patients (BBMT 2013; 19: 117).

**Aim of the study:** The aim of the present study is to update the outcome of our HAPLO program on 500 patients grafted between 2011 and 2017, in two transplant Units (Genova and Rome Gemelli).

**Patients:** Patients were selected for HAPLO grafts in the absence of a suitable HLA matched related or unrelated donor. The median age of the patients was 52 years (14-74), and 106 patients were over 60 years of age. Remission status was as follows: CR1 (37%), CR2 (25%) and advanced disease (38%). The median donor age was 34 years (18-67). The diagnosis was AML (35%), ALL (20%), MDS (18%), myelofibrosis (11%), non Hodgkin lymphoma (6%) other (10%).

**Conditioning regimens:** we used 2 myeloablative conditioning regimens, one chemotherapy based (n=423) including Thiotepa, Busulfan, Fludarabine (TBF) as described (BBMT 2013), and one radiation based (n=80) with full dose radiation (999-1200 rads) (TBI) and fludarabine (BBMT 2013). The TBF regimen was used with full dose Busulfan 3.2 mg/kgx3, or 3.2 mg/kg x2, for patients over 60 years of age. The median age for the TBF regimen was 55 years (18-74), whereas for the TBI it was 35 years (14-64). GvHD prophylaxis for all patients, was Cyclosporin (CsA) 2 mg/kg i.v. starting day 0, mycophenolate 2 gr/day p.o. starting day+1 to day+30, PT-CY 50 mg/kg day +3 and day+5. When possible CsA was tapered starting day +100 and discontinued day +180. All patients received unmanipulated marrow as a stem cell source.

**Failure to engraft:** the proportion of patients rejecting the graft was 0% for patients receiving TBI, 2.7% for TBF (BU3 days) and 6.7% for TBF (BU2 days). Seventeen patients received a second HAPLO graft with the Baltimore regimen, and 14 achieved trilineage recovery. Death due to rejection was overall 0.75%.

**GvHD:** The cumulative incidence of acute GvHD II-IV was 28% and of aGvHD grade III-IV 3%. The CI of moderate severe chronic GvHD was 18%.

**Cross sectional study 1 year post HAPLO:** At one year post transplant 88% of patients were off CsA and 83% were off steroids. The average Karnofsky score was 97%. Chronic GvHD was scored as absent (68.7%) minimal (24.8%), moderate (4.8%) and severe (1.4%). Chimerism was scored as full chimera, in 96% of patients.

**Outcome:** Non relapse mortality (NRM) at 4 years, was 16% for remission patients and 22% for patients with advanced disease (p=0.1). Relapse was 20%, 27%, 43% for patients in CR1, CR2, advanced disease (p<0.0001).

Actuarial 4 year survival was 72%, 54, 35% for patients in CR1, CR2, advanced disease. Survival was comparable for remission patients receiving either TBF (BU3) (72%) or TBF (BU2) (64%) , despite a significant age difference (44 vs 61 years).

**Conclusions.** We confirm very encouraging outcome of a HAPLO program using myeloablative conditioning , a modified PT-CY day+3+5, and CsA starting on day0. Engraftment, GvHD and disease control have been have been consistent across different age groups and diagnoses. Post-transplant interventions for patients with advanced acute leukemia are being designed.

# Novel Drugs and Approaches to Lymphoma Patients and the Role of Transplantation in 2019

**John M. Pagel**

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Over the last decade rapid therapeutic advances have changed the landscape of non-Hodgkin Lymphoma (NHL) and chronic lymphocytic leukemia (CLL) therapy. These disease have traditionally been treated using cytotoxic chemotherapy regimens in combination with anti-CD20 antibody treatment. The advent of oral targeted therapies, particularly B-cell receptor signaling inhibitors, BCL-2 inhibitors, and immune modulating agents, has provided generally well-tolerated and highly effective additional options that have come into widespread use in the front-line and relapsed settings. Additional agents are advancing in clinical development that continue to advance the field by increasing therapeutic choices with potentially more favorable risk-to-benefit profiles. With the rapid development of these novel therapies in relapsed NHL and CLL patients, many unanswered questions remain including the optimal sequence (first versus second line), duration, discontinuation and combination of these agents, and in particular where hematopoietic cell transplantation and cellular therapies fit in treatment algorithms. Since the field of NHL/CLL management has become much more complex we will focus on understanding the recent data and discuss many of the above questions and controversies important for how we approach NHL/CLL patients.

(FL) is one of the most common subtypes of indolent lymphoma. With the introduction of anti-CD20 antibody rituximab, prognosis of patients with FL has improved with a median survival of newly-diagnosed patients being over 20 years. However, most of the patients will have relapsed disease and patients who have relapse early after diagnosis or after completing first-line chemoimmunotherapy (POD24 or failure to achieve EFS12) have poorer prognosis compared with those without relapse during this period. Clinical implication of early progression varies according to patient's background, especially first-line treatment (ex R-CHOP vs R-bendamustine vs rituximab).

Treatment for FL is further evolving with the introduction of other novel agents and novel cellular therapies. One of recently introduced agents is obinutuzumab, a second generation type II anti-CD20 antibody. In randomized phase 3 trials, obinutuzumab in combination with chemotherapy was shown to improve progression-free survival (PFS) and PFS and overall survival (OS) in patients with FL in a first-line and relapsed/refractory setting, respectively. Non-chemo regimens have been introduced in the management of FL. In a randomized phase 3 trial, lenalidomide plus rituximab (R2) was shown to improve PFS compared to rituximab monotherapy in patients with relapsed/refractory indolent B-cell lymphomas. In another randomized phase 3 trial in newly-diagnosed FL with high-tumor burden, PFS with R2 was comparable to that with chemoimmunotherapy, although primary endpoint of CR/CRu rate at 120 week was not met in this trial. Phosphoinositide 3-kinase inhibitor (PI3K inhibitor) is promising new targeted agent for FL. Based on single-arm phase 2 trials, idelalisib, copanlisib, duvelisib have been approved by FDA as a third-line treatment option, although none of PI3K inhibitors have not shown clinical benefit in a randomized phase 3 trial or have not been approved in Japan. Inhibitor for enhancer of Zeste homolog 2 (EZH2), tazemetostat have been tested for patients with FL with or without EZH2 mutation in a phase 2 trial and promising results have been reported especially for patients with EZH2 mutation.

Several CD19-directed chimeric antigen receptor-transduced T-cell (CAR-T) therapies are being developed for B-cell malignancies and it has a potential of changing treatment paradigm. Recently, tisagenlecleucel (CTL019) has been approved for patients with relapsed/refractory DLBCL in Japan. Axicabtagene ciloleucel (Axi-cel, KTE-C19) has also been approved for relapsed/refractory DLBCL by FDA and EMA. CD19-directed CAR-T therapy is also being tested for relapsed/refractory FL.

Stem cell transplantation (SCT) including high-dose chemotherapy followed by autologous SCT and allogeneic SCT is still an important treatment option. Allogeneic SCT remains the only potentially curative treatment option for FL, but it has a high treatment-related mortality rate. However, with the development of new treatment option, indication for SCT will be changing.



# Clinical Significance of Mixed Chimerism after Allogeneic Stem Cell Transplantation

Hoon Kook

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Chimera originally was a fire-spitting monster in Greek mythology with the head of a lion, a tail of a serpent, and the body of a goat. The investigation of the genotype origin of post-transplant hematopoiesis are called chimerism analysis. For a long time, it was believed that complete donor chimerism (CC) is necessary to maintain engraftment after allo-HSCT. However, donor and recipient hematopoiesis may co-exist, a state of mixed chimerism (MC). The state of hematopoietic chimerism may change dynamically, from CC to MC or vice versa. And the MC state may show either "increasing donor MC" or "increasing recipient MC". Also, split chimerism may be used, if a patient's hematopoiesis is mixed only in different cell lines. Methods for chimerism analysis have been evolving from historical restriction fragment length polymorphism (RFLP), cytogenetics, red cell phenotyping and fluorescent in situ hybridization. PCR based amplification of variable number of tandem repeats (VNTR) or short tandem repeats (STR) has become the basis to study chimerism. Real-time PCR approaches and more recently digital PCR procedures allows accurate and absolute quantification of DNA.

Chimerism studies in clinical settings should be separated between nonmalignant and malignant diseases. For non-malignant diseases, such as severe aplastic anemia, inherited bone marrow failure syndromes, sickle cell disease, thalassemia, immunodeficiency, storage diseases and others, transplantation should provide stable and durable engraftment to improve hematopoietic function, to correct immune competence, and/or to improve the respective enzyme shortage. Thus, it is usually sufficient to implement a state of MC to improve the patients' well-being, rather than a mandatory state of CC. Less myeloablative conditioning is used in practice to minimize toxic side effects, but graft rejection or non-engraftment remains major causes of treatment failure. However, the risk of rejection in non-malignant patients showing MC depends on the diagnosis and on the conditioning regimen. Donor lymphocyte infusion (DLI) may be used to stabilize MC or even to convert to CC in many cases. However, the potential risk of inducing GvHD should be considered. In thalassemia patients, increasing recipient MC > 30% is associated with graft rejection and transfusion dependency. DLI might be beneficial in those cases with MC. In sickle cell disease 10% stable donor chimerism is necessary for effective treatment from a homozygous healthy donor, while at least 30% of donor chimerism is required from a heterozygous HbAS donor.

For malignant diseases a state of MC frequently facilitates recurrence of underlying leukemia. Immunotherapeutic interventions, eg, withdrawal of immunosuppression or transfusion of DLI, could convert MC to CC, restore graft-versus leukemia effect, and prevent overt hematological relapse. As a minimum residual disease (MRD) marker, chimerism analysis in the whole blood may not be suitable because of limited sensitivity. Chimerism analysis should be performed in cell populations, such as in the CD34+ cell fraction for AML or MDS, in the CD10, CD19, for precursor B ALL, or in the CD3, CD4, CD7, CD8 for T ALL. Serial and quantitative analysis of chimerism along with MRD analysis is crucial to identify patients at high risk of relapse. These strategies may serve as a platform for individual preemptive immunotherapy to prevent recurrence of underlying disease.

# How to Overcome Graft Failure after Allogeneic Stem Cell Transplantation

**Takehiko Mori**

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Graft failure remains to be one of the gravest life-threatening complications of allogeneic hematopoietic stem cell transplantation (HSCT). Primary graft failure is defined as the absence of initial donor cell engraftment after HSCT without evidence of disease relapse, and secondary graft failure as the loss of donor cells once after the initial engraftment. The incidence of graft failure ranges between 2-6%, which significantly differs among the transplant settings. The transplant settings at the highest risk for graft failure are cord blood transplantation and also allogeneic HSCT for non-malignant diseases such as aplastic anemia. In regard to cord blood transplantation, the significant impact of numbers of nucleated cells and CD34-positive cells in the infused unit on the achievement of engraftment have been demonstrated. In addition, the analysis by Japanese Cord Blood Banks showed that the presence of anti-HLA antibodies had a negative effect on the neutrophil and platelet recovery after unrelated cord blood transplantation. Based on these findings providing useful information in selecting cord blood unit, the outcome of cord blood transplantation has been improved.

The working group of aplastic anemia (adults) of Japan Society of Hematopoietic Cell Transplantation (JSHCT) have been focusing on the graft failure after allogeneic HSCT for aplastic anemia. One of the established options for the graft failure after allogeneic HSCT is the second transplantation. In unrelated HSCT, the urgent second transplant for graft failure can only be performed from a different donor. Therefore, to elucidate the outcome of this critical setting, we retrospectively analyzed the outcome of second HSCT using cord blood for the graft failure after the first allogeneic HSCT for aplastic anemia. The survival was about 40% with a more favorable outcome by mycophenolate mofetil-based GVHD prophylaxis and fludarabine-based regimen with low-dose total body irradiation. Another issue to be discussed is the graft failure with the donor-type chimerism after allogeneic HSCT for aplastic anemia. Recently, JSHCT performed a nationwide survey about the graft failure after allogeneic HSCT for aplastic anemia. Patients with secondary graft failure with mixed or complete recipient-type chimerism and those with secondary graft failure with complete donor-type chimerism showed significantly inferior survival to those without. Multivariate analysis demonstrated that use of fludarabine was associated with both types of secondary graft failure. Such current topics of the graft failure which have been evaluated by the JSHCT database and activities, mostly in aplastic anemia, will be summarized.



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# Joint Symposium



# Identification of High-Risk Acute Myeloid Leukemia

Hiroki Yamaguchi

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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a useful treatment aimed at cure of acute myeloid leukemia (AML). However, non-relapse mortality (NRM) in allo-HSCT is as high as around 20%, and allo-HSCT therefore needs to be applied appropriately based on a consideration of the prognosis. The prognostic factors in AML include age, white blood cell count at initial presentation, and chromosomal abnormality. The advent of the next-generation sequencer has enabled prognostic stratification to additionally take account of gene mutations. It has been suggested that the gene mutations *nucleophosmin member1* (*NPM1*), *CCAAT/enhancer-binding protein α* (*CEBPA*), and *fms-like kinase 3*-internal tandem duplication (*FLT3-ITD*) act as prognostic factors in AML of normal karyotype, and these mutations are also used in the prognostic classification of each guidelines. In this symposium, my presentation will show about *FLT3-ITD* low allele ratio (AR) and *KIT* D816 mutation that are a poor prognostic factor in AML.

## 1. *NPM1* mutation-positive AML with *FLT3-ITD* low AR is not a favorable prognosis

*FLT3-ITD* gene mutation is observed in approximately 25% of AML patients. In clinical terms, *FLT3-ITD* gene mutation is associated with risk of relapse from complete remission (CR), and has been reported to carry an unfavorable prognosis. For this reason, allo-HSCT in the first remission (CR1) is recommended in *FLT3-ITD*-positive AML patients of transplant-eligible age. In recent years, however, it has been reported that the inclusion of *FLT3-ITD* AR may make possible more detailed prognostic stratification in *NPM1* mutation-positive AML. In response to these findings, the the European Leukemia Net (ELN) proposed a new prognostic classification in 2017. In the opinion of ELN, *NPM1* mutation-positive AML with *FLT3-ITD* AR of below 0.5 has a favorable prognosis, and allo-HSCT in CR1 is not actively recommended. Although it involves only a certain proportion of *FLT3-ITD*-positive cases, this is the first time that *FLT3-ITD*-positive AML has been classified in the favorable prognosis group, and there appears to be a fair number of clinicians who view the ELN recommendation with skepticism.

Our study therefore aimed to examine the prognostic impact of *FLT3-ITD* AR and explore whether allo-HSCT is indicated in *FLT3-ITD*-positive AML. We studied 147 patients with *FLT3-ITD* gene mutation-positive AML, dividing them into those with low AR and those with AR of 0.5 or above (high AR), and examined the prognostic impact according to allo-HSCT in CR1. Although *FLT3-ITD* AR and *NPM1* mutation are used in the prognostic stratification, we found that *NPM1* mutation-positive AML with *FLT3-ITD* low AR was not associated with favorable outcome (overall survival (OS) 41.3%). Moreover, patients in this group that underwent allo-HSCT in CR1 had a significantly more favorable outcome than those that did not (relapse free

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survival (RFS):  $p=0.013$ ; overall survival (OS):  $p=0.003$ ). Multivariate analysis identified allo-HSCT in CR1 as the sole favorable prognostic factor (RFS:  $p<0.001$ ; OS:  $p<0.001$ ). Our study found that prognosis was unfavorable in *NPM1* mutation-positive AML with *FLT3*-ITD low AR where allo-HSCT was not carried out in CR1.

## **2. D816 mutation alone of all KIT mutations is an unfavorable prognostic factor in core binding factor (CBF)-AML**

AML displaying the chromosomal abnormalities  $t(8;21)(q22;q22)$  and  $inv(16)(p13.1q22)$ ,  $t(16;16)(p13.1; q22)$  is known by the general name CBF-AML, and CBF-AML is classified as having a favorable prognosis. Mutations of the *KIT* gene were found in only around 4-5% of all AML cases, but in approximately 30% of patients with CBF-AML. In CBF-AML, *KIT* mutation has been identified in some reports as an unfavorable prognostic factor for early relapse and survival. On the other hand, there are also reports finding that *KIT* mutation in CBF-AML has no impact on prognosis. One potential reason why the reported prognostic impact of *KIT* mutation in CBF-AML differs between studies is that CBF-AML cases with  $t(8;21)$  and those with  $inv(16)$  have differing clinical profiles; another is that it is sometimes not possible at initial presentation to detect minor clones with *KIT* mutation using the direct base sequencing method; an additional factor is that *KIT* mutation occurs at various locations on the gene. Our group has also found, using a highly sensitive mutation detection method known as mutation-biased PCR (MB-PCR) to detect *KIT* mutations, that cases with D816V mutation at initial disease onset may have a high relapse rate. The aim of our study was to clarify the significance of the individual *KIT* mutations as prognostic factors in CBF-AML in which CR1 had been achieved. We retrospectively analyzed 136 cases of CBF-AML that had gone into complete remission (CR). *KIT* mutations were found in 61 (45%) of the patients with CBF-AML. D816, N822K, D816 and N822K, and other mutations of the *KIT* gene were detected in 29 cases (21%), 20 cases (15%), 7 cases (5%), and 5 cases (4%), respectively. The rate of relapse-free survival (RFS) and overall survival (OS) in patients with D816 and with both D816 and N822K mutations was significantly lower than in patients with other or with no *KIT* mutations (RFS:  $p<0.001$ , OS:  $p<0.001$ ). Moreover, stratified analysis of the chromosomal abnormalities  $t(8;21)$  and  $inv(16)$  showed that D816 mutation was associated with a significantly worse prognosis. In a further multivariate analysis of RFS and OS, D816 mutation was found to be an independent risk factor for significantly poorer prognosis. In the present study, we were able to establish that, of all *KIT* mutations, D816 mutation alone is an unfavorable prognostic factor.

# Prediction of Post-Transplant Outcomes in Acute Myeloid Leukemia

**Je-Hwan Lee**

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Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative treatment for acute myeloid leukemia (AML) with high-risk features. However, HCT is accompanied by a significant rate of non-relapse mortality (NRM), which is mainly caused by graft-versus-host disease (GVHD), infection, and major organ failures. The NRM and survival may reflect a complex entanglement of the factors related to the patient (age, comorbidities, etc.), disease (disease status, cytogenetic or molecular features, etc.), donor (HLA matching degree, donor type, donor age, etc.) and transplantation procedure (conditioning intensity, stem cell origin, etc.). Prediction of post-transplant outcomes is essential to select optimal patients who will benefit from HCT, to guide patient counseling before HCT, and to stratify the patients into different risk groups in clinical studies. Over the last two decades, several prognostic scoring systems have been developed to predict the risk of NRM or relapse, and survival probabilities after HCT.

The European Society for Blood and Marrow Transplantation (EBMT) risk score was introduced for the patients with chronic myeloid leukemia, and then its utility was also verified in other diagnoses. The system includes five components of donor, stage, age, sex match, and time from diagnosis to HCT. The Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI), a modification of the Charlson Comorbidity Index, was modeled to effectively capture comorbidities and predict HCT outcomes in a cohort of patients with various hematologic malignancies at a single institute. The score ranges from 0 to 29, and three categories (0, 1 to 2, and 3 or more) correspond to NRM of 14%, 21%, and 41%, respectively, in the original publication. Subsequently, the utility of the index was validated in patients with AML. The EBMT score and HCT-CI are based on a standard statistical approach, such as the Cox proportional hazards model. Using the Alternating Decision Tree (ADT) machine learning algorithm, the European researchers developed a new prognostic model, the Acute Leukemia (AL)-EBMT score, for prediction of mortality after allogeneic HCT in a large cohort of acute leukemia patients (n=28,236). The AL-EBMT score includes ten variables of disease stage, Karnofsky performance status, age, time from diagnosis to HCT, conditioning regimen, donor, annual allogeneic HCT center experience, year of HCT, donor-recipient serostatus combination, and diagnosis. Other prognostic scoring systems include the Disease Risk Index (DRI), Pretransplantation Assessment of Mortality (PAM), Umbilical Cord Blood Transplantation score, and some modifications of previous scores such as HCT-CI/Age, refined DRI, Disease Risk Comorbidity Index (DRCI), and HCT-composite risk (HCT-CR). The Center for International Blood and Marrow Transplantation Research (CIBMTR) score and factors from a retrospective analysis by EBMT predict survival after unrelated donor transplantation for AML patients with active disease.



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Despite the usefulness of various available prognostic models for post-transplant outcomes, the optimum prognostic scoring system remains elusive. A better understanding of the molecular features of AML and the introduction of novel biological, immunomodulatory, and molecularly targeted agents might influence on the indication, timing, and procedures of transplantation. Accordingly, current prognostic models should be repeatedly re-evaluated and improved in specific settings.

# Personalized Application of SCT for Adult AML

**Shingo Yano**

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Although more than 70% of patients with acute myeloid leukemia (AML) achieve remission, a significant number relapse. The survival rate among patients aged  $\leq 65$  years is 40%. Allogeneic hematopoietic stem cell transplantation (SCT) offers the most effective prevention of relapse and has significant overall survival (OS) benefits for patients with intermediate- or poor-risk AML in first complete remission (CR1). SCT from an HLA-matched related donor (MRD) is significantly beneficial for OS in patients with AML in CR1; however, only approximately one-third of patients have a suitable MRD. An HLA 8/8-matched unrelated donor (MUD) is one of the alternative options because SCT from an MUD results in a similar OS to that from an MRD. Umbilical cord blood (UCB) is another option and a national network of cord blood banks has been established in Japan. UCB has the advantage of immediate availability and the absence of risks to the donor; however, the higher associated risk of NRM is problematic. We retrospectively analyzed a large number of SCT cases for AML based on the nationwide registry of the Japan Society of Hematopoietic Cell Transplantation (JSHCT). We analyzed 1,561 patients who underwent HCT from an HLA-matched related donor (MRD) (n=699), HLA 8/8 matched unrelated donor (MUD) (n=372), or umbilical cord blood (UCB) (n=490). The results of a multivariate analysis showed that the risk of relapse was significantly lower in MUD recipients (HR = 0.75, 95%CI: 0.57–0.97,  $P = 0.03$ ) and UCB recipients (HR = 0.64, 95%CI: 0.50–0.83,  $P < 0.01$ ) than in MRD recipients, however, HCT from UCB (HR = 1.28, 95% CI: 1.07–1.52,  $P < 0.01$ ) had an inferior prognostic impact on OS. HCT from UCB (HR = 1.87, 95%CI: 1.46–2.38,  $P < 0.01$ ) was significantly increased the risk of NRM, and the high rate of NRM negates the advantage of the lower risk of relapse. No significant differences were observed in the hazard ratio of OS between MUD and MRD recipients. The intensity of conditioning (reduce-intensity conditioning: RIC, myeloablative conditioning: MAC) regimens did not influence relapse or OS in patients with AML in CR1 in the multivariate analysis (Yano et al. Bone Marrow Transplant in press).

MAC regimens have traditionally been used for patients aged  $\leq 55$  years, and cyclophosphamide/ total body irradiation (CY/TBI) and busulfan/ CY (BU/CY) are widely known conventional MAC regimens for AML. The addition of high-dose cytarabine (HDCA) to CY/TBI may improve OS compared to CY/TBI by suppressing relapse without non-relapse mortality (NRM). AML and MDS working group of JSHCT analyzed a cohort study to compare prognosis of HDCA/CY/TBI (n=617) and CY/TBI (n=312) who underwent allo-SCT from UCB for adults with AML and MDS. OS was significantly superior in the HDCA/CY/TBI group (adjusted HR = 0.56, 95% CI: 0.45–0.69,  $P < 0.01$ ), relapse was lower (HR = 0.49, 95% CI: 0.30–0.80,  $P < 0.01$ ), and tumor-related mortality

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was lower (HR = 0.50, 95% CI: 0.38-0.67,  $P < 0.01$ ) in SCT from UCB. Unadjusted subgroups analysis revealed that the superiority of OS in the HDCA/CY/TBI group was observed both standard-risk AML and high-risk AML. HDCA/CY/TBI did not increase NRM in the whole cohort (HR = 0.94, 95% CI: 0.67-1.33,  $P = 0.73$ ) (Arai et al. Blood 2015;126: 315). AML and MDS working group of JSHCT subsequently analyzed the prognosis of HDCA/CY/TBI (n=435) and CY/TBI (n=1667) who underwent allo-SCT from a related donor (RD) or an unrelated donor (UD) for myeloid malignancies. OS was not improved in the HDCA/CY/TBI group (adjusted HR = 1.14, HR: 0.96-1.34,  $P = 0.13$ ) in SCT recipients. Relapse was not reduced by the addition of HDCA (HR = 0.90, 95% CI: 0.63-1.30,  $P = 0.58$ ) and NRM was significantly higher in the HDCA/CY/TBI group (HR = 1.48, 95% CI: 1.15-1.91,  $P < 0.01$ ) (Arai et al. J Hematol Oncol 2015; 8: 315).

The outcomes of SCT in patients with non-remission AML remain unsatisfactory. We developed an intensified conditioning regimen consisting of BU/CY/TBI for patients with myeloid malignancies with non-remission at the Jikei University Hospital. Twenty-eight patients (AML 22, CML in accelerated or blastic phase 6) received BU (8 mg/kg), CY (120 mg/kg), and TBI (10 Gy) followed by SCT from RD (n=9), UD (n=11) or UCB (n=8). Median follow-up for survivor was 127.3 (7.5-207.5) months and median age of patients was 37 (17-55) years. The 2-year actuarial OS and event-free survival rates were 50% and 32%, respectively. The 5-year OS was 32%. The cumulative incidence of relapse and NRM rates at 2-year were 30% and 15%, respectively. These results indicated that the BU/CY/TBI provided durable remission with acceptable NRM.

We conclude that SCT from MRD is significantly beneficial for OS in patients with AML CR1, and MUD is the best alternative to an HLA identical MRD. UCB is an alternative option if neither an MRD nor MUD are available or when patients need to receive urgent HCT for poor-risk AML in CR1. The intensity of conditioning regimens did not influence OS in patients with AML in CR1, and RIC appears to be an acceptable option for patients with AML in CR1. HDCA/CY/TBI regimen is superior to that of CY/TBI regimen in myeloablative SCT from UCB but not from RD or UD, particularly those who are high-risk AML. Intensified conditioning regimen consisting of BU/CY/TBI may improve OS without augmentation of NRM for the patients with non-remission AML.

# Tailored Therapy for Pediatric AML

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Outcome of pediatric acute myeloid leukemia (AML) has improved significantly in the contemporary era. Recent cooperative trials report event-free survival (EFS) and overall survival (OS) rates of approximately 50-60% and 60-70% respectively. Such advances have been due mostly to improvements in supportive care and hematopoietic cell transplantation (HCT), rather than major changes in AML chemotherapy. A key feature of all current pediatric AML trials which may also have contributed to better treatment outcome is the designation of risk group for each patient, based on factors such as genetic and cytogenetic abnormalities with prognostic relevance, and response to initial chemotherapy. Such risk group classification allows for the implementation of treatment strategy based on patient prognosis; a chemotherapy only treatment plan is feasible for patients with favorable prognosis, while allogeneic HCT is reserved for those with high risk features.

Since 2012, our institution has participated in a multi-center prospective trial in pediatric AML (AML 2012), incorporating risk group classification based on genetic risk and response to initial chemotherapy. Patients are initially classified into three risk groups (low, standard, high) based on genetic features. Subsequent designation of an overall prognosis group (favorable, intermediate, poor) is based on the genetic risk group, as well as response to the first two courses of chemotherapy. Distinguishing features of this protocol include the designation of patients with low risk core binding factor (CBF) AML to standard risk if they also have concurrent KIT mutation, allogeneic HCT based on reduced intensity conditioning (RIC) for intermediate prognosis group patients if they have a human leukocyte antigen (HLA) well-matched donor, and proceeding with allogeneic HCT in all poor prognosis group patients, with a haploidentical donor if necessary.

The results of this trial have so far been comparable to other cooperative trials in pediatric AML with 5-year EFS of 59% and 78% respectively.

# HMGB1 Control on Chemokine Induced Inflammation

**Mariagrazia Uguccioni**

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A vast range of *in situ* experiments have revealed that a variety of chemokines and HMGB1 can be concomitantly produced at target sites of leukocyte trafficking and homing. The development of inhibitors specifically targeting chemokine receptors has been a logical and attractive goal ever since the discovery of the chemokine system. While it is well established the effects of different chemokines singly, much less was known about the potential consequences of the concomitant expression of multiple chemokines, and their interaction with other inflammatory molecules, such as HMGB1. Most of the competitive chemokine receptor antagonists developed by all major pharma companies have been disappointingly unsuccessful when tested in clinical trials, and as a matter of fact the only two small molecule inhibitors approved to this point do not target inflammation as an indication. We strive at understanding the complex scenario we are faced with in pathological conditions, which would vanish the activities of therapies targeting a single chemokine or a chemokine receptor. Nonetheless, the chemokine system remains a promising biological target for the development of new therapeutic tools for the treatment of chronic diseases, but some limitations hamper the efficacy of conventional competitive inhibitors, and call for innovative approaches.

The demonstration that chemokines have additional regulatory mechanisms started with the identification of natural chemokine antagonists. We showed that several chemokines could also antagonize non-cognate chemokine receptors, by abrogating cellular responses via the occupancy of the chemokine receptor-binding pocket. Chemokine not only act as natural antagonist, but can form chemokine heteromeric complexes, activating one type of chemokine receptor enhancing the responses induced by the selective agonist. Some of these heterocomplexes can even preserve chemokines from degradation initiated by the atypical chemokine receptor ACKR2.

In addition to chemokines that synergize with members of the same family, we have describe how the alarmin HMGB1 is able, by complexing with CXCL12, to enhance CXCR4 responses. The different redox forms of HMGB1 can influence CXCL12-induced responses or trigger cytokine production. In fact, only the reduced form of HMGB1 can form a complex with CXCL12. All these studies, performed by us and other groups, have highlighted the details of the natural chemokine synergism, including studies on receptor dimerization, and relevance *in vivo*.

We have demonstrated recently that the CXCL12/HMGB1 heterocomplex is present in Rheumatoid Arthritis

(RA), and its activity correlates with the disease activity score, DAS28. Both HMGB1 and CXCL12 have been shown to be massively upregulated in the circulation of patients with RA.

Furthermore, inflammatory conditions are associated with the release of reactive oxygen species, which alters the redox status of the microenvironment. Our study has revealed that the innate immune system in patients with RA is prone to respond to the CXCL12/HMGB1 heterocomplex, and put in place mechanisms for maintaining HMGB1 in the reduced form. We have observed that high levels of Thioredoxin and Thioredoxin Reductase are present in blood vessels and synovial fluids, and are released by monocytes, representing an attempt of reducing the oxidative stress in niches of the microenvironments. The activity of the Thioredoxin system becomes detrimental when HMGB1 is released, because the protein is preserved in its reduced form, favouring the formation of the heterocomplex with CXCL12 and contributing to fuel the influx of inflammatory monocytes into the synovium.

These studies encourage and inspire us to further assess the structure of the heterocomplexes and reconsider those pathological conditions in which persistent immune activation can modify the responses to the innate and adaptive immune system in order to identify novel markers for therapeutic intervention.

## Insight into Strategies to Target HMGB1 Fueling Inflammation

**Andrea Cavalli**

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Protein–protein interactions (PPIs) are receiving increasing interest, much sparked by the realization that they represent druggable targets. Recently, we successfully developed a peptidic inhibitor of the CXCL12/HMGB1 interaction. During inflammatory reactions, the production and release of chemotactic factors guide the recruitment of selective leukocyte subpopulations. HMGB1 and the chemokine CXCL12 are both released in the microenvironment and can form a heterocomplex, which exclusively acts on the chemokine receptor CXCR4, enhancing cell migration, thus potentially exacerbating the immune response. An excessive cell influx at the inflammatory site can be diminished by disrupting the heterocomplex. To date, only few inhibitors of the CXCL12/HMGB1 interaction have been described. We will describe a novel computational pipeline for the fast screening of large libraries of peptides, which allows the identification of a restricted number of potential inhibitors of protein-protein interaction. By applying a multistep docking procedure, we selected the 13 peptides with the highest predicted affinity to the CXCL12-binding pocket of HMGB1. The in vitro assessment of their efficacy lead to the identification of HBP08, a peptide able to inhibit the activity of the heterocomplex both on CXCR4 transfected cells and on human monocytes. Furthermore, HBP08 binds to HMGB1 with a measured  $K_d$  of  $0.79 \pm 0.06 \mu\text{M}$ , representing the strongest HMGB1-binding molecule known to date. We propose the described computational protocol as a useful tool, which can be broadly applied for the development of powerful antagonists of known pathogenic molecular interactions.

# A Global Perspective on Cell and Gene Therapies of Relevance to Transplanters

**John Rasko**

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Over the next five years a possible 900% increase in Gene and Stem Cell Therapy approvals has been forecast. Immunotherapies including checkpoint inhibitors and CAR-T cells have captured the attention of many scientists, physicians and cancer sufferers. However, the convergence of substantial incremental technical advances towards combined cell and gene therapy has led to improved clinical outcomes in immune deficiencies, haemoglobinopathies, blindness, immunotherapies and other inherited diseases. An audit of cell, tissue and gene products with marketing authorization in 2018 worldwide identified 44 unique products, 37 of them are cell and tissue therapies (84%) and mainly autologous (55%).

Since the first human clinical trial using gene technology in 1989, there have been nearly 3000 approved clinical trials worldwide. Highlights in the clinical cell & gene therapy field of direct relevance to Blood Marrow Transplantation will be discussed with special reference to thalassemia and graft versus host disease.

In May 2019 the EMA approved Zynteglo for the treatment of patients 12 years and older with transfusion-dependent  $\beta$  thalassaemia (TDT) who do not have a  $\beta^0/\beta^0$  genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available. We have recently updated results from the completed phase 1/2 Northstar and ongoing phase 3 Northstar-2 studies in patients with transfusion dependent  $\beta$ -thalassemia and non- $\beta^0/\beta^0$  genotypes.

Although advances in red blood cell (RBC) transfusion and iron chelation have improved the prognosis of patients with transfusion dependent  $\beta$ -thalassemia (TDT), allogeneic hematopoietic stem cell (HSC) transplantation is the only curative therapy. LentiGlobin gene therapy is being evaluated in patients with TDT and contains autologous CD34+ cells transduced ex vivo with the BB305 lentiviral vector (LVV) encoding  $\beta$ -globin with a T87Q substitution.

As of 14 September 2018, 10 and 16 patients with TDT and non- $\beta^0/\beta^0$  genotypes have been treated in Northstar (16-34 yrs; follow-up 36.0 [29.3-48.1] months) and Northstar-2 (8-34 yrs; follow-up 9.3 [0.7-20.4] months), respectively. All patients who have >2 months follow-up have achieved neutrophil and platelet engraftment. In Northstar, 8/10 patients with non- $\beta^0/\beta^0$  genotypes achieved transfusion independence (TI; weighted average hemoglobin [Hb]  $\geq 9$  g/dL without RBC transfusions for  $\geq 12$  months). The median duration of TI was 38 (21.2-43.6) months and all responses are sustained. Median weighted average total Hb during TI was 10.2 (9.3-13.2) g/dL. In Northstar-2, 10/11 patients with  $\geq 3$  months follow-up stopped RBC transfusions with Hb of 11.1-13.3 g/dL comprising 7.7-10.6 g/dL gene therapy-derived Hb, HbA<sup>T87Q</sup>, at last visit. Two



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patients achieved TI. Five of 6 patients with  $\geq 12$  months follow-up had improved myeloid:erythroid ratios (1:5.6-1:2.2 to 1:1.3-1.1:1).

The most common non-hematologic grade  $\geq 3$  adverse events post-infusion ( $\geq 3$  patients with non- $\beta^0/\beta^0$  genotypes in either study) were stomatitis, febrile neutropenia, irregular menstruation, epistaxis, pyrexia, and veno-occlusive liver disease. There was no transplant-related mortality or vector-mediated replication of competent lentivirus. No single integration site contributed to  $\geq 30\%$  of all integration sites at any time, this finding being consistent with polyclonal hematopoiesis.

We have recently completed the first trial of iPSC-derived Mesenchymal stromal cells in Steroid-Resistant Acute GvHD. MSCs have been widely investigated as a treatment for graft versus host disease (GvHD), but with mixed results. Factors such as MSC donor variability and the effects of prolonged culture expansion may contribute to inconsistent or disappointing outcomes. The novel Cymerus<sup>TM</sup> manufacturing process facilitates virtually limitless production of well-defined and consistent MSCs from a single human iPSC bank, using clonogenic progenitor-based technology. This avoids both inter-donor variability, batch-to-batch variation and the need for prolonged in vitro expansion of MSCs. We have conducted a multi-centre, open label study of Cymerus MSCs (CYP-001) in adults with steroid-resistant acute GvHD. The primary objective was assessment of safety and tolerability, while the secondary objective was efficacy, based on best responses by Day 28/Day 100 and overall survival. This is the first completed study worldwide with any iPSC-derived product. It has yielded encouraging safety and efficacy data, which support further clinical development of Cymerus iPSC-derived MSCs for GvHD and other indications.

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# Current Review of Immunocellular Therapy Against Cancer

**Jaeseung Lim**

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We now live in the era of Immunotherapy for cancer treatment. Many combinations of immune-controlled antibody drugs such as immune-check point inhibitors are being investigated. Tumor-specific antibodies have already been used for cancer treatment. These treatments are all affected by either change of tumor microenvironment or marking of tumor target and by killing tumors through the immune cells.

Recently the outstanding effects of CAR-T opened a new era in cancer treatment. However, their astonishing efficacy of tumor killing by CAR-T was limited to the blood cancer and reported several severe side effects. Therefore, competition is very high to overcome the limitation of CAR-T treatment for solid cancers. Various approaches to reduce side effects and to improve the killing efficiencies are being tried.

Nevertheless, autologous immune cell treatment is still attractive for cancer treatment. This approach has been criticized for questioning the statistical significance of efficacy and the potency of the produced cells for each individual. Therefore, allogeneic approach is being tried now from iPS cells or pluripotent stem cells.

Tumor is not a simple matter and not homogeneous. Even after the removal or killing of tumors, we need to surveillance well to maintain healthy. Therefore, the immune system in the body should work properly and balanced.

This talk will be reviewed for various approaches of immunocellular therapy for cancer treatment.

# NK Cell Therapeutics beyond CAR-T Therapy as An Immuno-Oncology Drug

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Allogeneic NK cells have been used their activity for hematologic cancer by hematopoietic stem cell transplantation. During the last decades, anti-cancer activity of *ex vivo*-expanded NK cells was demonstrated in several studies, both *in vitro* and *in vivo*. Previously, *ex vivo*-expanded allogeneic NK cells from healthy unrelated donor showed potent anti-tumor activity with tolerable toxicity profiles in several xenograft models. Random donor derived *ex vivo*-expanded NK cells can be a useful and safe treatment against cancer without any significant AEs. Allogeneic NK cell can induce host immune responses including T cell activation, Treg/MDSC reduction. At the same time, immune responses from host can reject transplanted NK cell, too. Targeting strategy using antibody combination or CAR insertion into NK cell can increase the efficacy of NK cell.

To enhance the efficacy of antigen specific T cell, new genetically modifying technology like chimeric antigen receptor (CAR) technology can be emerged. The CD19-CAR-T cell reports dramatic tumor responses in malignant and recurrent blood cancer patients. NK cells are attracting attention as an alternative to CAR T which show side effects and high COGs. NK cell is one of option to solve the problem in adverse effect in CAR-T therapy and to facilitate commercial use.

In cooperation with many of advanced technology, NK cell therapy also has been developed as allogeneic immune cell therapeutics. Based on mass production of NK cells, the development of next generation NK cell therapy with genetic modification is underway.

## Next Generation CAR-T

**Renier Brentjens**

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T cells may be genetically modified to express chimeric antigen receptors (CAR) targeted to antigens expressed by tumor cells. Recently published reports support the novel approach of treating cancer with patient derived T cells genetically modified to express artificial T cell receptors targeted to tumor associated antigens. Initial clinical trial outcomes of patients with B cell malignancies treated with autologous T cells genetically modified to express a CAR specific to the CD19 antigen, expressed on most B cell malignancies, demonstrate that this approach may ultimately prove to be a promising therapeutic intervention which will potentially dramatically alter the standard of care in these malignancies. Treatment of patients with CD19 targeted CAR T cells have resulted remarkable remission rates in relapsed B cell acute lymphoblastic leukemia (B-ALL). Specifically, based on currently updated clinical outcomes, we have achieved >85% CR rates in adult patients with relapsed B-ALL treated with CD19 targeted CAR T cells which far exceed historical expectations. Further, by deep sequencing analysis, most treated patients were MRD- after CAR T cell therapy. Significantly, remissions were observed in both patients with overt morphological residual disease at the time of therapy as well as in patients with only residual MRD+ disease. To this end, we will present novel data on a next generation of CAR T cells, termed "armored CARs" further genetically designed to overcome an immune suppressive tumor microenvironment through further genetic modification of CAR T cells.

# Allogeneic SCT and TKI for the Treatment of Adult Ph+ ALL

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Translocation (9;22) or *BCR-ABL* fusion gene is detected in approximately 25% of adults with acute lymphoblastic leukemia (ALL). Historically, treatment results of Philadelphia (Ph)-positive ALL were very poor and the patients' prognosis dismal. The relapse rate was very high and probability of long-term survival did not exceed 10% in patients treated with standard chemotherapy and 30-35% in those undergoing allogeneic hematopoietic stem cell transplantation (alloHSCT).

The introduction of the *BCR-ABL*-directed tyrosine kinase inhibitors (TKIs) in the front-line therapy of Ph-positive ALL has increased complete remission rates to more than 95%, improved the quality of response and duration of remission. However, without alloHSCT most of the patients ultimately relapse and therefore transplantation from either related or unrelated donors remains a standard of care and should be considered for all eligible patients.

Although the use of TKIs is associated with better disease control pre-transplant, relapses after alloHSCT remain a major problem being an important reason of treatment failure. Relapse rates are particularly high among patients with *BCR-ABL* transcripts detectable after alloHSCT. Strategies to reduce the incidence of relapse include post-transplant maintenance with the use of TKIs, which may be either prophylactic or pre-emptive, i.e. administered in case of detectable minimal residual disease (MRD). Patients should be evaluated for the presence of *BCR-ABL* transcript and for the presence of ABL kinase domain mutations prior to alloHSCT and after engraftment. Patients with detectable MRD after alloHSCT should be started on TKI treatment as soon as possible. Imatinib at initial dose of 400 mg/day is the first choice of TKI. Second or third generation TKI (dasatinib, ponatinib) should be used in case of resistance to imatinib or the presence of ABL kinase domain mutations either prior to alloHSCT or after alloHSCT. In addition, they should be considered in case of MRD-positivity detected within 3 months after alloHSCT or at level  $>10^{-3}$ , or if *BCR-ABL1* transcript levels remain detectable after 6-8 weeks of post-transplant imatinib. Patients with the history of CNS involvement should be treated with dasatinib. The treatment should be given for at least 12 months of continuous MRD-negativity. Individual adjustments may be needed in case of severe toxicity.

# Allogeneic HCT and TKI for the Treatment of Adult Patients with Ph-Positive ALL: Korean Experiences

**Jae-Ho Yoon and Seok Lee**

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Use of imatinib combined with chemotherapy as a first-line treatment has demonstrated improved complete remission (CR) rates and increased applicability to allogeneic hematopoietic cell transplantation (allo-HCT); thus, allowing better survival in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-positive ALL). Catholic Hematology Hospital previously conducted a phase 2 trial of allo-HCT following first-line imatinib-based chemotherapy, and the results showed a positive impact of imatinib on transplantation outcome (1, 2). However, a substantial proportion of patients with an extended follow-up continued to die as a result of leukemia relapse. Therefore, an improved strategy to induce more effective leukemic cell clearance was clearly needed with emerging second generation tyrosine kinase inhibitors (TKI). Thus, Korean ALL working group conducted a phase 2 trials of allo-HCT or TKI maintenance following first-line dasatinib (3) or nilotinib (4) combined with multi-agents chemotherapy and achieved similar treatment outcomes compared to previous imatinib trials. At present in Korea, National Health Insurance only permits the use of imatinib as a frontline therapy, followed by dasatinib (only from second-line) and ponatinib (only from third-line) in a sequential order only when drug resistance or intolerance to previous TKI is observed.

In the era of TKI and measurable residual disease (MRD)-targeted treatment, the role of allo-HCT in Ph-positive ALL became more controversial especially in patients who achieve MRD-negativity after TKI with or without conventional chemotherapy. However this approach is possible only when a sufficient level of sensitivity for MRD measurement is guaranteed because we still experience large differences in MRD results between the institutions. Therefore, we still suggest allo-HCT should be considered in Ph-positive ALL as a post-remission therapy even in patients with complete molecular response (CMR).

Although myeloablative conditioning (MAC)-HCT remains the best curative option for Ph-positive ALL, a significant proportion of patients still experience non-relapse mortality (NRM), especially older patients. Therefore, between eradication of residual disease for relapse prevention and lowering NRM, the principle for decision of conditioning intensity is yet to be elucidated especially in patients with CMR. Thus, reduced intensity conditioning (RIC) regimens have been studied in several groups which showed higher relapse rate but lower NRM. Although RIC transplants were older, subsequent survival outcomes were not different between MAC and RIC regimens. Catholic Hematology Hospital previously conducted phase 2 trials and showed that RIC can be an alternative choice allowing sufficient graft-versus-leukemia effect with less toxicity in older patients or those with comorbidities in CR1 (5, 6) followed by recent report which compared

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long-term outcomes of RIC with MAC, particularly focusing on the pre-HCT MRD kinetics-based role of conditioning intensity for adult Ph-positive ALL in CR1 (7). This data revealed there were no significant different clinical outcomes between RIC and MAC regimens, even in patients with poor molecular response at pre-HCT period and we suggested RIC is a valid alternative choice for long-term disease control and worthy of further investigation in prospective trials for adult Ph-positive ALL in CR.

However, we still cannot consider allo-HCT in elderly patients or in patients with severe comorbidity. Compared with Ph-negative ALL, Korean ALL working group data revealed the possible favorable impact in elderly patients with of Ph-positive ALL in the TKI era (8). This data showed longer relapse-free survival and better overall survival and multivariate analysis indicated that Ph-positive ALL is an independent good prognostic factor for survival in patients older than 60 years.

We expect that more sensitive MRD measurement may open the era of attenuated treatment strategy without allo-HCT, and TKI combined with recently introduced target immunotherapies are available in near future for patients with Ph-positive ALL.

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# Radiation or Drugs? Allogeneic Stem Cell Transplantation for Children with ALL – The European Experience

**Christina Peters**

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The majority of patients with childhood acute lymphoblastic leukaemia (ALL) have nowadays an excellent chance to be cured by multimodal chemotherapy. However, patients with the very high risk ALL (HR-ALL) or patients who have relapsed have a significantly worse prognosis compared to other patients with ALL. These patients require additional therapeutic approaches after achieving remission. Allogeneic haematopoietic stem cell transplantation (HSCT) can effectively induce immunological antileukemic control in patients with ALL by means of the graft-versus-leukemia effect (GVL) and is now standard of care. During the last decade, many patients with an indication for SCT were treated within prospective clinical trials in order to ensure best clinical practice and to acquire valid outcome data. As a consequence, treatment related mortality was reduced to less than 10%.

SCT indications have to be defined prospectively and must be re-evaluated and reconfirmed in intervals dependent on modifications and improvements of the chemotherapeutical approaches of the frontline and relapse protocols. Some risk factors for a dismal prognosis in childhood ALL are known even at diagnosis (e.g. cytogenetic characteristics, time and site of relapse). Additionally, response to induction treatment measured by morphology and/or detection of minimal residual disease (MRD) has a strong predictive value and defines SCT indications. The indications for HSCT in children with ALL in CR1 is limited to the subpopulation of high risk ALL. Most study groups define these patients as having estimated EFS of less than 50%. ALL patients, who experience an early marrow relapse, still have a dismal prognosis when treated with conventional chemotherapy. Although nearly 90% achieve a second remission, most of them subsequently develop progressive disease. Both matched sibling donor HSCT and unrelated donor HSCT are clearly indicated in these patients since the outcomes are similar. If a matched sibling or a well-matched unrelated donor cannot be identified, other types of donors such as cord blood, mismatched unrelated donors, or haploidentical family donors are option for the very high risk patients.

The choice of the conditioning regimen has a significant impact on the survival after SCT. The standard for many years was a combination of total body irradiation (TBI) and cyclophosphamide. Within the BFM-transplant trials it was shown that the conditioning with total body irradiation plus etoposide (TBI/VP16) was superior to TBI/cyclophosphamide (Peters et al., JCO 2015). It is evident that irradiation and particularly TBI is one of the biggest burden for children and adolescents as the risk for secondary malignancies is significantly higher compared to pharmacological conditioning. However, busulfan/ cyclophosphamide have



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not shown the same antileukaemic efficacy. Therefore the current standard backbone for the biggest European prospective trial consists of fractionated TBI (12Gy) and etoposide which was randomised between a combination of fludarabine/thiotepa/intravenous busulfan or treosulfan ("FORUM-trial"). After an interim analysis of the randomised arm the randomisation was closed as TBI/VP16 showed significant better OS and EFS compared to both chemo-conditioning regimen. The study is now conducted as prospective international multicentre trial without randomisation and recruited more than 950 patients from 31 countries.

# Pediatric Acute Lymphoblastic Leukemia in Korea

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The cure rate of acute lymphoblastic leukemia (ALL) in children dramatically improved over past 5 decades from zero to about 80-90%. The main cause of improvement is owing to the development of chemotherapy by multicenter clinical trial of large study groups with the understanding of leukemia biology. Despite the improvement of outcomes in pediatric ALL, there were some remained problems in Korea about 10 years ago. First the nationwide outcome of high risk ALL was not so satisfactory compared with Western countries and the chemotherapeutic dosages of some drugs in Western protocols were not fit for Korean patients. Second, the outcome of very high risk ALL was not so satisfactory. Third, the outcome of relapsed patients was very poor with only 20% survival rate. To improve the nationwide outcome of ALL in children and adolescent, multicenter clinical studies had been conducted for high risk, very high risk and relapsed ALL from 2005 to 2013 which was supported by a grant from National R&D Program for Cancer Control, Ministry for Ministry for Health & Welfare and from 2014 new trials were begun for the same risk groups. The results of previous and ongoing Korean pediatric ALL clinical trials and our efforts to improve the outcomes of HSCT for ALL will be presented in this talk.

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## Registry and Clinical HLA NGS Typing- Implication on Donor Selection

**Neng Yu**

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# State of the Art and Current Challenges of Donor Registries in the World

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WMDA strives that patients worldwide have equal access to high quality cells for transplantation from donors whose rights and safety are protected. Our mission is to promote global collaboration and the sharing of best practices for the benefit of stem cell donors and patients. WMDA works in four different areas:

- Optimising Search, Match & Connect: provide a global platform that facilitates access to the most suitable stem cell source for a transplant patient
- Supporting Global Development: support members to develop and grown, so that more transplant patients find the most suitable match
- Promoting donor care: assure that the rights and safety of stem cell donors are promoted and protected
- Ensuring Quality: promote product quality and global collaboration through accreditation and standardisation

## Current status of Unrelated Donor Hematopoietic Stem Cell Transplantation in Korea

**Joon Ho Moon, Keon Hee Yoo, Jung Hwa Nah, Sung-Yong Kim, Hyoung Jin Kang, June-Won Cheong, Nack-Gyun Chung, Seong-Kyu Park, Yanghwa Lee, In-Ho Kim**

Academic committee of Korea Marrow Donor Program (KMDP)

The Korea Marrow Donor Program (KMDP) has been providing the gift of life for many patients who are in need of hematopoietic stem cell transplantation (HSCT) since its establishment in 1994. The KMDP started peripheral blood stem cell (PBSC) collection in 1998 and incorporated cord blood (CB) in 2001. The number of volunteer donors has grown to 344,848 by the end of Dec 2018, and the steady growth of our donor pool resulted in higher matching rate of over 90% for domestic patients. The total number of HSCT facilitated by the KMDP has reached above 3,000 by February 2012 and 5,320 by the end of December 2018. Currently about 320 transplants a year are performed through the KMDP both nationally and internationally.

Over the past 25 years, transplants have been performed for a wider variety of diseases, being myeloid malignancies as the most common indication. There has been a dramatic increase in the use of PBSC as the graft source. In order to commemorate the 5000th Transplantation Anniversary of the KMDP, we reviewed the outcome of 5283 unrelated HCT coordinated by the KMDP from 1995 to 2018, including 1173 bone marrow transplantation (BMT), 3645 PBSCT and 465 CBT. The analysis was possible for 3728 transplants. The median age of recipients was 28 years (range 4 months to 72 years), and 2187 (58.7%) were male. Acute leukemia (n=2406, 64.5%) was the most common indication followed by severe aplastic anemia (n=443, 11.9%) and myelodysplastic syndrome (n=387, 10.4%). The median age of donor was 28 years (range 19 to 55 years), and 69% were male. Five-year overall survival (OS) rate was 57.2% for overall patients with 55.3% and 73.0% for acute leukemia and benign hematologic diseases, respectively.

Working together with many transplant centers, collection and apheresis centers, coordinators and other staffs cross the borders; the KMDP could benefit over 5,000 patients. We sincerely appreciate their dedicated supports and hope the prosperity of our alliance.

# Design the future of Japan Marrow Donor Program (JMDP)

**Shinichiro Okamoto**

Division of Hematology, Keio University School of Medicine, International Committee, JMDP

Japanese society is rapidly aging and the proportion of younger generation is getting smaller. This dynamic change in our population movement has significant impacts on not only the activity of allogeneic hematopoietic stem cell transplantation but also the operation of donor registries. Currently JMDP address this issue from several different viewpoints in collaboration with the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and the Japanese Data Center for Hematopoietic Cell Transplantation (JDCHCT).

First, we estimated the optimal size of donor registry/cord blood banks (CBB). When donor pool was 300,000, the possibilities of obtaining 10 donor candidates for 8-allele matched or 7-8 allele matched donor were 30% and 51%, respectively. Considering the recent improvement of 1-allele mismatched transplantation, donor pool size of 300,000 with complete HLA-A,-B,-C,-DRB1 information would be reasonable. We also clarified that the 0.1 million increase from the current 0.4 million donor pool resulted in only 5% increase the chance to locate fully or one antigen mismatched donors. This emphasized the importance of maintaining the donor pool with high retention rates.

Regarding the quality of donor pool, most transplant physicians prefer male/younger donors for their patients when multiple donor options exist. However, significant recruitment of female donors continues worldwide and appears to be increasing. Although a diversity of ethnic backgrounds is not an issue in Japan, the relative importance of targeted recruitment of male donors as compared to donors who are younger remains an issue for individual recruitment organizations to address. Our recent studies clearly showed that the survival superiority of younger unrelated donor over older donors, but the gender of donor does not significantly affect the transplant outcomes. Ethical considerations regarding the rights and wishes of donors will also need to be addressed to maintain the goodwill and support from motivated and well-meaning females who are not specifically targeted.

Timely access to hematopoietic stem cells is crucial to improve the transplant outcome, especially for acute leukemia. Understanding causes of potential delay in the coordination and transplant process will help transplant physicians and donor registries reduce the time to transplant. JMDP is facilitating several projects for shortening the search turnaround time in collaboration with JSHCT. Those include the incorporation of web based monitoring system for donor coordination, the creation of centralized transplant/collection/apheresis centers network as part of a national project.

It is clear that HCT is one of the most successful cellular therapies in the 20th century. Current HCT is significantly safer, more effective, and is available for a wider variety of indications. This success supports the

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use of allogeneic HSCT as an attractive platform for testing promising cancer therapeutics. An improved understanding of the genetics and molecular basis of hematologic diseases will enable us to switch from traditional chemo-radiotherapy to more specifically targeted immune-therapeutics or innovative cellular therapies. The use of HSCT to facilitate tolerance in solid organ transplant is another area of active clinical research. Further, the clinical use of "induced pluripotent stem cells" to generate blood specific lineage holds great promise. We believe that donor registries are one of the critical assets to facilitate innovative and promising cellular therapies and should positively consider how to facilitate the approaches while harmonizing our activities with regulatory authorities.

# Current Status and Future Expectation of Buddhist Tzu Chi Bone Marrow Donor Registry

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Buddhist Tzu Chi Foundation formally founded Buddhist Tzu Chi Bone Marrow Donor Registry in October 1993. With the collective effort by Buddhist Tzu Chi Stem Cells Center (BTCSCC) and its volunteer workers, the Registry successfully performed the first case of unrelated bone marrow stem cells donation in May, 1994. In 1997, the Center established its Immunogenetics Laboratory which undertakes HLA testing function for potential bone marrow stem cell donors joining the Registry's recruitment, confirmatory HLA typing for selected donors intended to donate their bone marrow stem cells and for blood borne disease patients requiring bone marrow stem cell transplantation domestically or internationally. In 2001, Tzu Chi Cord Blood Bank, Peripheral Blood Stem Cell Collection Center and Bone Marrow Transplantation Center were established. They are responsible for receiving, processing and cryopreservation of umbilical cord blood intended for hematopoietic stem cell transplantation, harvesting of bone marrow hematopoietic stem cells through apheresis procedure and perform hematopoietic stem cell transplantation therapy for patients with hematological diseases respectively. With devotion joined by a team of over 10 thousands Tzu Chi volunteer workers, today, Buddhist Tzu Chi Stem Cell Center has over 440,000 potential volunteer bone marrow donors enrolled in the Registry and a panel of over 12,000 units of cryopreserved cord blood units in its storage reservoirs.

As of July 31, 2019, a total of 5405 cases of bone marrow stem cell donations have been provided for hematopoietic stem cell transplantation for patients in 31 countries and regions. On average, nowadays, the Registry offers one case of bone marrow stem cell donation to transplant hospital in every day of the year. For the Tzu Chi Cord Blood Bank, so far, a total of 126 units of cord blood have been delivered to 108 patients in 11 countries and regions. In the past nine years, Tzu Chi Cord Blood Bank offered cord blood units for patients in Taiwan for transplantation for free. A total of 23

patients have been benefited. To assist transplant patients in Taiwan with financial disadvantage, our Center provides financial assistance to cover portion of their medical costs incurred by transplantation procedure. From 2005 to 2017, a total of 48 million Taiwanese dollars were offered for 481 Taiwanese patients.

Since its establishment in 1997, the Tzu Chi Immunogenetics Laboratory has evolved its HLA typing platform from serological methodology to sequence-based typing ever since 2004 and recently next generation sequencing technique has been employed to become another HLA typing protocol. With the DNA typing procedures, many novel HLA alleles in various HLA loci are being revealed in Taiwanese population.



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The BTCSCC attained its WMDA (World Marrow Donor Association) accreditation general status in 2010 and its advanced WMDA accreditation in 2015. Further, the Centre received a Bronze Award and a Silver Award from Symbol of National Quality accreditation in 2016 and 2018 respectively.

The BTCSCC looks forward to collaborate with international bone marrow donor registries to enhance the quality and efficiency on hematopoietic stem cell product services to benefit transplant patients worldwide. Joint effort with other registry and institutes to upgrade scientific publication is in progress. We are equally committed to recruit younger potential donors to enroll to Tzu Chi Bone Marrow Donor Registry and to increase ethnic diversity among our newly recruited potential donors.

# Challenges of Unrelated Bone Marrow Donor Registries

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Patients with serious blood diseases who failed chemotherapy might still be rescued with haematopoietic stem cell (HSC) transplantation. However, as not all patients have matched and suitable family members as HSC donors, unrelated bone marrow donor registry provides important resources for them through identification of HLA matched volunteer donors either locally or internationally, as alternate HSC source. Indeed, the registry has emerged its role as an important national coordinating body in managing a local database of potential voluntary donors, searching and matching patients with local and international donors, procuring HSC donation for HSC transplantation.

Over the years, unrelated bone marrow donor registry continues to expand its works and at the same time improve safety and quality in both donors and HSC. Quality framework and regulatory compliance are two main elements that need to adhere. Besides, as HLA matched and suitable donors may only be available from overseas registries, international cooperation is gaining importance to serve the patients.

There are a number of challenges encountered in the provision of registry services. Mismatch in the number of registered voluntary donors to the demand and its under-presentation of ethnic minorities are frequently encountered. Moreover, aging donor and donation limitations due to body size and preference of type of donation are of particular concerns of which the latter two are particularly seen in Asian countries. Therefore, concerted efforts among registries have been made to address them.

Besides, with significant changes in the use of cord blood and development in cell therapies, the role of unrelated bone marrow donor registry will continue to evolve further for the ultimate benefits of the patients.

## Experience with Second Allo-HCT in Hematologic Disorders among Adult Patients

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Allogeneic hematopoietic stem cell transplantation (Allo-HCT) is potentially curative for variety of benign and malign hematological disorders. However, disease relapse is the major cause of treatment failure after allo-HCT, which is associated with dismal outcome. Relapse rates in hematological malignancies after allo-HCT which varies greatly depending in the underlying disease and its state, have been reported to be 63% **(1)**, and even up to 70% in myeloid malignancies **(2)**.

The therapeutic approach for this group of patients is challenging and of variable success. The options of treatment are limited, and its choice depends upon several factors, such as primary diagnosis, disease burden, performance status, organ function and presence of graft-versus-host disease (GvHD). Salvage chemotherapy, supportive care, withdrawal of immune suppression, donor lymphocyte infusion (DLI) and second allo-HCT are major options for these patients. Patients who experience significant toxicity or adverse events from the first allo-HCT are commonly offered supportive care, whereas other eligible patients may receive DLI or second allo-HCT. But, no standard strategy has been established thus far to improve survival **(3)**. Enhancing the graft-versus-tumor (GvT) effect by means of DLI, given as a single treatment approach, carries only modest chance of achieving a response with a 2-year survival of 21% vs 9% for patients not receiving DLI **(4)**. Its efficiency is variable and depends among other causes. DLI is generally effective in chronic myeloid leukemia (CML), but less frequently in other malignancies **(5)**. In addition, patients who relapse with high disease burden and having active GvHD would not generally be considered for DLI. Therefore, a second allo-HCT is a valuable option for these patients. On the other hand, a recent retrospective study compared overall survival (OS) after a second allo-HCT or DLI in relapsed AML after a first allo-HCT showed comparable OS between the groups. Results demonstrated similar OS between the second allo-HCT and DLI groups at 2 years (26% vs 25%) and 5 years (19% vs 15%) respectively. However, two characteristics appeared associated with improved survival either second allo-HCT or DLI; having a complete remission (CR) prior to salvage therapy and longer time to relapse after first allo-HCT. Patients who relapsed less than 6 months after first allo-HCT 5-year OS was 9% with second allo-HCT and 4% with DLI **(6)**.

Although concerning second allo-HCT in the literature are rare and generally limited to retrospective studies with low number of patients, for select patients relapsed after allo-HCT probably the best treatment option for long term survival is still a second allo-HCT. But, second allo-HCT are more complex than the first ones. Transplantation-related morbidity and mortality are usually higher owing to accumulating toxicity, and its prognosis is very poor with a 5-year OS rate ranging between 10-30% **(1,2,7-10)**. Therefore, in recent years

most of the studies performed in this era were aimed to find out the critical prognostic factors for defining the patients who would gain benefit from the second allo-HCT. In a large EBMT analysis of 2632 hematologic malignancies who underwent second allo-HCT relapsing after the first allo-HCT, only 15% of the patients remained relapse-free until 5 years after the second allo-HCT. Patients with CML had better OS than the others. Low disease burden, longer remission duration, younger age, absence of GvHD and later year of transplantation were the factors associated with better survival in a multivariate analysis **(11)**. A retrospective multicenter study from Japan evaluated the prognostic factors in 60 patients who experienced relapse after first allo-HCT and underwent second allo-HCT. The OS at 2-year, non-relapse mortality (NRM) and relapse mortality (RM) were 30.3%, 40.9% and 28.8%, respectively. Matched related donor, reduced intensity conditioning (RIC) regimen and low disease burden were found to be significant as a favorable prognostic factor for OS **(12)**. The Grupo Espanol de Transplante Hematogetico presented a retrospective cohort of 116 patients diagnosed with acute myeloid leukemia, myelodysplastic syndrome and myeloproliferative neoplasms who consecutively underwent a second allo-HCT for disease relapse. OS at 5-year was 32%. Multivariate analysis identified active disease status ( $p < 0.001$ ) and a second allo-HCT < 430 days after the first allograft as factors for poor prognosis, whereas the use of HLA-identical sibling donor for the second allo-HCT was defined as a good prognostic factor. Their study confirmed active disease and early relapse as a dismal prognostic factor for a second allo-HCT. Using a different donor did not appear to change the outcome, but using an HLA-identical sibling donor for a second allo-HCT appears to be associated with better survival **(8)**. The Cooperative German transplant Group performed a retrospective registry study on 179 second allo-HCT given for relapse after first allograft, using identical or alternative donors for second allo-HCT. They showed second allo-HCT can induce 2-year OS in approximately 25% of the patients. Remission duration and disease burden were found to be prognostic factors in multivariate analysis. Outcome of second allo-HCT was better after matched related first allo-HCT than after matched unrelated donor first allo-HCT (2-year OS; 37% vs 16%, respectively,  $p = 0.042$ ). Selecting a new donor for second allo-HCT did not result in a relevant improvement in OS compared with second allo-HCT from the original donor **(10)**.

CIBMTR studied outcomes of 1788 AML patients relapsing after allo-HCT to identify factors associated with longer post-relapse survival. Only, 23% of the patients survived more than 1-year post-relapse. In multivariate analysis, lower mortality was significantly associated with longer time from first allo-HCT to relapse ( $p < 0.0001$ ) and using RIC regimen in first allo-HCT ( $p = 0.0002$ ). In contrast, inferior survival was associated with age > 40-year, active GvHD at relapse, adverse cytogenetics, mismatched URD and use of cord blood for first allo-HCT. Second allo-HCT success was similar with MRD or URD **(13)**. An EBMT series of 286 patients described long term outcomes with only 10% 10-year and 7% LFS. RM and NRM were 53% and 35% respectively. Complete remission at second allo-HCT, relapse more than 10-months after the first allograft and TBI in the second allo-HCT were found to be favorable factor for long term survival **(14)**. ASBMT studied 351 relapsed patients after first allo-HCT. Risk factors for mortality after relapse were shorter time to relapse, higher disease risk index at second allo-HCT, myeloablative conditioning and GVHD. OS at 3-year was only 19% **(15)**. In another study investigating 92 patients who underwent second allo-HCT, showed ECOG performance score before second allo-HCT as an independent factor for survival. On univariate analysis,

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longer remission of duration and reduced conditioning intensity were also significant on favorable survival **(16)**.

Similar results were also identified in children who were underwent second allo-HCT due to the relapse **(17,18)**. A retrospective EBMT-PDWP study including 373 children, showed OS was 38% at 2-year and 29% at 5-year. Favorable prognostic factors for OS and LFS included > 12 months between transplantations, and cGvHD after first allo-HCT, complete remission (only ALL) and age >12-year (only AML). Findings were more consistent over time in the ALL group **(17)**.

Haploidentical allo-HCT using in vitro T-cell depleted grafts as salvage therapy in patients with disease relapse after first allograft was also showed to be feasible with OS at 1 and 2-year were 32% and 14%, respectively. Patients with CR before second allo-HCT had a very favorable OS of 41.7% at 2-year **(19)**. Haploidentical second allo-HCT have been previously reported and should be considered a treatment option in this hapless group of patients **(9)**.

In summary, given that relapse after first allograft is a dismal station, some subset of the patients can achieve long-term remission following second allo-HCT. Longer remission duration after the first allo-HCT (> 6-12 months), complete remission before second allo-HCT, RIC regimen (using TBI, if not used previously in first allograft) and good performance status are associated with improved OS and lower TRM. Available data does not support time loss for searching of alternative donor. Novel treatment approaches like immunotherapies and cellular therapies need to be investigated to achieve CR before second allo-HCT and to improve survival following allo-HCT.

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# Experience of Second Allogeneic Transplantation in Korean Pediatric Patients with Hematologic Malignancy, Focusing on Post-Transplantation Outcome and Transplantation-Related Morbidity

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Allogeneic hematopoietic cell transplantation (HCT) is potentially curative for a variety of benign and malignant hematological diseases. A major cause of treatment failure post-allogeneic HCT is disease relapse, which can occur in up to 30% of patients in adult study. Post-transplantation relapse is still associated with a dismal prognosis and its optimal treatment remains unclear. Second allogeneic HCT is a salvage option in these patients; however, data demonstrate that only a minority of relapsed patients eventually undergo second allogeneic HCT. Relapsed patients who undergo second transplant have demonstrated an improved survival compared to those receiving only supportive care, although a significant proportion of these patients relapse post-second HCT. Parameters such as younger patient age, favorable performance status, longer time between first and second HCT, and low disease burden have been associated with improved outcomes in adult data.

Another major indication for second allogeneic HCT is graft failure. Primary graft failure is considered when the patient never recovers from neutropenia post-HCT while secondary graft failure occurs when donor cells are lost after the initial post-HCT engraftment. In Japan study, among the children with severe aplastic anemia who received 2<sup>nd</sup> HCT, the 5-year overall survival (OS) and failure-free survival (FFS) after the second transplantation were 82.9% and 81.2%, respectively. FFS was significantly better when the interval between the first and second transplantation was >60 days than when it was ≤ 60 days.

Data concerning second allogeneic HCT in the literature are scarce and are generally limited to retrospective studies with limited numbers of patients.

This presentation will review the experience of second allogeneic transplantation in Korean pediatric patients with hematologic malignancy, focusing on post-transplantation outcome and transplantation-related morbidity.

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# Scientific Session





# Long Term Follow-Up of a Phase 2 Clinical Trial to Induce Tolerance in Living Donor Renal Transplant Recipients

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Thirty-seven patients were transplanted in a phase 2 protocol to establish chimerism to induce tolerance in up to 0 of 6 matched related and unrelated recipients of living donor renal allografts (KTx). The protocol is based upon tolerogenic CD8<sup>+</sup>/TCR<sup>-</sup> facilitating cells (FC) and nonmyeloablative conditioning. Recipients were conditioned with fludarabine (30 mg/m<sup>2</sup> days -5, -4, -3), cyclophosphamide (50 mg/kg day -3 and +3), 200 cGy TBI (day-1) followed by KTx (day 0). G-CSF mobilized peripheral blood mononuclear cells were apheresed from the donor >2 weeks before kidney transplantation, processed to remove graft-versus-host disease (GVHD)-producing cells yet retain CD34<sup>+</sup> cells and FC, and cryopreserved until transplantation on day +1 after kidney transplantation. Immunosuppression (IS) consisted of mycophenolate mofetil and tacrolimus. 36 patients have reached at least 1 year of follow up (range 12-105 months) and are the focus of this analysis. Patients ranged in age from 18-65 yrs. Enrollment was agnostic to degree of HLA match; 2 were 6/6 and 3 5/6 matched related using high resolution allele level typing, with the remainder 4/6 to 0/6 matched related (n=15) or unrelated (n=16). Two of the recipients were renal re-transplants. Tacrolimus/MMF IS was weaned and discontinued at 1 year if chimerism (>50% whole blood and T cell), normal renal function and normal kidney transplant biopsy were noted. 34 of 36 subjects exhibited peripheral blood donor chimerism at one month post KTx. Durable chimerism allowing for full IS withdrawal developed in 26 (time off IS from 1- 88 months); the majority (23/26) showed >95% donor whole blood/T cell chimerism. Three have exhibited stable-mixed chimerism ranging between 40% - 60%. Three patients failed to develop chimerism. Transient chimerism occurred in 8 patients. Durably chimeric patients retained chimerism after removal of IS, remain rejection-free without donor-specific antibody (DSA) and show immunocompetence. None have had to resume immunosuppression. Transiently chimeric subjects resumed endogenous hematopoiesis and are maintained on low-dose IS with stable renal function. There have been two cases of GVHD: one grade 2 lower GI acute GVHD that developed during conversion from tacrolimus to sirolimus that responded to steroids; this patient has developed moderate chronic GVHD of the skin. He is off IS. The second presented late following development of severe gastrointestinal symptoms and manifested treatment-resistant lower GI GVHD with associated tissue-invasive CMV colitis that proved fatal at 11 months post-Tx. A second subject death occurred in a heavy (>100 pack yr) smoker who developed advanced stage lung cancer 4.5 years after Tx. A third subject developed pneumococcal sepsis > 4 years after transplant. He had not undergone the recommended pneumococcal vaccination post HSCT. There have been two additional kidney graft losses, both related to early infections. Overall patient survival is 91.8% and death censored graft survival 94.1%. These rates compare favorably to treatment-related mortality after standard of care renal transplantation. In summary, high levels of durable chimerism and tolerance with a low (5.5%) incidence of GVHD has been achieved in up to 0 of 6 matched related and unrelated recipients of FC + KTx.

# Tolerance Induction in Kidney Transplantation with Simultaneous Bone Marrow Transplantation: SMC Experience with Protocol optimization

Jae Berm Park

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In the field of organ transplantation, tolerance induction has been considered as a way to achieve life-long allo-graft functioning. We have performed combined bone marrow and kidney transplantation in HLA-mismatched patients to induce transient mixed chimerism and donor-specific tolerance. From December 2011 to June 2019, 9 HLA-mismatched patients received CBMKT for tolerance induction.

The initial conditioning regimen (Protocol 1) consisted of cyclophosphamide, rituximab (375 mg/m<sup>2</sup>, 7 and 2 days before transplantation), anti-thymocyte globulin (rATG), and thymic irradiation. Tacrolimus and steroids were used for the maintenance of immunosuppression (IS). The regimen was subsequently modified by reducing cyclophosphamide dose and adding fludarabine (Protocol 2), which was further modified by reducing fludarabine / rATG dose as well as early conversion of tacrolimus to rapamycin (Protocol 3). Mixed chimerism, detected by the short-tandem repeat method, was achieved transiently in all recipients for 3-20 weeks.

Protocol 1 was complicated with 'engraftment syndrome' and side effect of CP, although one of two subjects successfully discontinued his IS for 14 months. In three subjects treated with Protocol 2, IS was successfully discontinued for longer than 43 months in one recipients, two of them were suffered from BK nephritis. By reducing the dose of fludarabine (Protocol 3), three recipients successfully discontinued their IS for 7-50 months. (One maintained IS for 3 months post-transplantation.) De novo DSA was not detected in all the recipients during the follow-up periods even in the patients who experienced acute rejection or graft failure. Although further modification of the conditioning regimen is still necessary to reduce the risk of infectious complications, our clinical trial has shown that renal allograft tolerance can be achieved by induction of transient mixed chimerism with combined donor bone marrow transplantation

# Combined Organ and Bone Marrow Transplantation for Induction of Allograft Tolerance

**Tatsuo Kawai**

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There have been two clinical indications for combined kidney and bone marrow transplantation (CKBMT); CKBMT for patients with hematologic malignancies who developed end stage renal disease (ESRD) and for ESRD patients without malignancy.

CKBMT for the patients with hematologic malignancy and ESRD is aiming at both treatment of malignancy and induction of allograft tolerance. Therefore, the protocol is intended to induce persistent full donor chimerism. At Massachusetts General Hospital (MGH), CKBMT from HLA-matched donor has been performed for the treatment of hematological malignancies, mainly myeloma, with ESRD. So far, 12 HLA matched CKBMT was performed with the longest patient survival exceeding 20 years. This approach has now been extended to HLA haploidentical transplant. Six CKBMT from haploidentical donors, five of whom were conditioned with fludarabine, cyclophosphamide and total body irradiation; graft-vs.-host disease (GVHD) prophylaxis included post-HCT cyclophosphamide, tacrolimus and mycophenolate mofetil. There were no cases of grades II-IV acute GVHD and one case of moderate chronic GVHD by 12 months. One patient experienced relapse of multiple myeloma at 30 months after HCT and died four years post-transplant. Overall, four of six patients remain alive, without disease relapse and with long-term renal rejection-free survival.

CKBMT has also been performed in regular ESRD patients without malignancies for induction of allograft tolerance. Four medical centers have been conducting clinical trials of CKBMT with different strategies/protocols.

The approach developed by the Stanford group is based on decades-long basic and clinical studies using a total lymphoid irradiation (TLI) conditioning regimen, which attempts to induce renal allograft tolerance via persistent mixed chimerism. The conditioning protocol for CKBMT consists of TLI and rabbit anti-thymocyte globulin (rATG), followed by peripheral blood stem cell transplantation. Calcineurin inhibitor (CNI), mycophenolate mofetil (MMF) were tapered over 6 to 14 months. Chimerism was induced in 28/29 HLA matched CKBMT, and immunosuppression (IS) was discontinued in 24 patients. Among these 24 recipients, 10 with stable chimerism and 14 with transient chimerism were off IS for 2 to 113 months. The most recent cohort included 19 recipients of HLA-haplotype- matched kidneys. Although persistent chimerism during the first 12 months was achieved in 9 of 18 patients followed for at least 1 year, their chimerism is IS dependent and none of the mismatched patients have been successfully withdrawn from IS drugs.

The approach for tolerance by the Northwestern University group is through induction of persistent donor

chimerism. Their conditioning included fludarabine, cyclophosphamide (CP), total body irradiation, followed by the living donor kidney transplant. A "mobilized" peripheral blood mononuclear cell product was processed to contain defined quantities of T cells, CD34+ cells and facilitator (FCRx) cells, and cryopreserved until administration the day after the kidney transplant. Tacrolimus and MMF are weaned off over the 12 months. Among the first 31 subjects who have reached >12 months, durable donor chimerism was established in 23 subjects and IS was successfully discontinued in 22 subjects with immunosuppression-free survival ranging from 8 to 81 months. Full donor chimerism was observed in 19/22 subjects. Two subjects lost their renal allografts within the first year posttransplant related to the development of opportunistic infections. GVHD was observed in two subjects with one patient died due to Grade 3 GI GVHD at 11 months after transplantation.

At MGH, tolerance has been induced via induction of transient mixed chimerism. The conditioning regimen for 10 HLA-haplotype mismatched kidney transplantation patients without malignancy consisted of CP, anti-CD2 mAb, and thymic irradiation. On Day 0, kidney transplantation was performed, followed by whole donor bone marrow cells. CyA was administered postoperatively and then slowly tapered off over 9 to 14 months. The regimen was subsequently modified by adding peri-transplant rituximab injections. Transient mixed chimerism for up to 3 weeks was induced in all recipients, without any evidence of GVHD. IS was successfully discontinued in 7/10 recipients. Four have remained off IS with normal kidney function, after more than 10 to 17 years. In the other three, IS was resumed after 5, 7, and 8 years due either to recurrence of the original kidney disease or development of chronic rejection.

The protocol at the Samsung Medical Center was summarized as modification of the MGH protocol and was intended to induce tolerance via transient mixed chimerism. The initial conditioning regimen consisted of CP, rituximab, and anti-thymocyte globulin. Because of CP toxicity and engraftment syndrome, the regimen was revised by reduction of the CP dose by adding fludarabine. Since this revised regimen is complicated by BK virus infection, the regimen was further modified by reduction of the fludarabine and ATG dose. With the last modification, all three recipients successfully discontinued IS for >3-41 months.

Improving the consistency of tolerance induction with less morbidity, extending the approach to deceased donor transplantation and inducing tolerance of non-renal transplants, are critical next steps for a wider range of clinical applications.

# Immune Tolerance in Kidney Transplantation: Korean Experiences

**Jae-Ho Yoon**

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The short-term clinical outcomes of kidney transplantation (KT) have been improved significantly with advances in the utility of immunosuppressive agents and the development of immune-monitoring methods for sensitization and rejection. However, long-term use of immunosuppressive agents might result in infectious complications, secondary malignancy, and metabolic derangements such as metabolic syndromes and cardiovascular complications. In addition, currently used immunosuppressive agents do not prevent chronic rejection, which is the most common cause of late loss of grafted kidney. Over the last several years, trials for induction of immune tolerance to overcome such complications have been attempted in solid organ transplantation. Indeed, successful cases of immune tolerance induction through mixed chimerism after combined hematopoietic cell transplantation (HCT) and KT have been reported in a few centers. However, there are still many obstacles and limitations to the HCT and KT combination protocols for real-world practice, and long-term immune tolerance was found only in a minor proportion of patients in those trials.

First, the role of mixed chimerism in the maintenance of immune tolerance has not been fully established. Although it is evident that development of mixed chimerism is essential for the induction of early-stage immune tolerance in solid organ transplantation, whether durable mixed chimerism is necessary for permanent immune tolerance is still controversial. In a previous report from Massachusetts General Hospital, an immune-tolerant state was maintained despite transient mixed chimerism. The proposed mechanism for that was the expansion of regulatory T-cell population and peripheral depletion of donor-specific T-cells. In contrast, another group proposed that durable mixed chimerism was essential for the long-term maintenance of immune tolerance. Indeed, the underlying mechanism for the maintenance of immune tolerance remains to be elucidated.

The second issue is a method for monitoring of immune tolerance. Detection of mixed chimerism does not always reflect a real state because persistence of immune tolerance was observed even after the disappearance of macrochimerism. However, there is no available method to confirm the level of tolerance exactly even after the disappearance of mixed chimerism. In Catholic Hematology Hospital and the department of Nephrology in Seoul St. Mary's hospital, we experienced three cases of simultaneous HCT and KT for the induction of immune tolerance. We will introduce our induction protocol in each case with clinical courses and outcomes.

# Tolerance Induction in Kidney Transplantation: The Stanford Experience

**John Scandling**

Stanford University, USA

Kidney transplantation is the superior renal replacement therapy. Transplantation requires immunosuppression. Immunosuppression carries risk of infection and malignancy. Immune tolerance allows transplantation without immunosuppression. Creation of hematopoietic cell chimerism is the current pathway to kidney transplant tolerance. Tolerance and successful immunosuppressive drug withdrawal has been accomplished with combined hematopoietic cell and kidney transplantation in living donor transplantation, in HLA-matched and in HLA-mismatched donor/recipient pairs.

The conditioning regimen for the HCT in the Stanford protocol is total lymphoid irradiation and antithymocyte globulin, which is administered following the kidney transplantation. The HCT, consisting of CD34+ hematopoietic progenitor cells and CD3+ cells, which are necessary to engraftment, is performed on day 11 following kidney transplantation. Multi-lineage mixed chimerism is evident in the peripheral blood within weeks. If mixed chimerism persists for a minimum of six to nine months, without evidence of rejection or graft versus host disease, immunosuppressive drug taper over several months is begun. A surveillance transplant kidney biopsy is performed just prior to complete drug cessation. In the HLA-matched trial, loss of mixed chimerism during drug taper does not cease the taper, whereas in the HLA-mismatched trial, loss of mixed chimerism now does cease the taper.

The HLA-matched trial began in 2005. Of the 29 study participants, 24 developed mixed chimerism of sufficient duration to allow drug cessation. Twenty-three of the 24 achieved rejection-free transplant kidney survival, now up to over 10 years off drug. Of the 24, approximately two-thirds lost chimerism after the first year. Of those who lost chimerism, one sustained an acute rejection episode after being off drug for four years. The rejection was treated successfully, and the patient is doing well on maintenance immunosuppression four years later. Five patients did not achieve sufficiently lasting chimerism to allow drug withdrawal.

The HLA-mismatched trial began in 2010. All recipients share one HLA-haplotype with their donors. Of the 25 recipients, 22 are over one-year post-transplant. Ten of the 22 developed mixed chimerism of greater than a year's duration, and 9 of the 10 were tapered to immunosuppressive monotherapy. During the second year, three of the 9 were withdrawn from monotherapy and two were reduced to sub-therapeutic monotherapy. All of these five returned to maintenance immunosuppression, three due to acute rejection and two due to loss of chimerism. Consequently, drug cessation is no longer attempted in the absence of whole blood donor chimerism of at least 20%.

The protocol has been well tolerated and has proven to be safe, with 54 transplant recipients since 2005. There

has been no GVHD. Neutropenia has required treatment in a small number. There has been two cases of hemolytic anemia, and two cases of "engraftment" syndrome. There have been four deaths and four transplant kidney losses, three to recurrent kidney disease and one to chronic pyelonephritis. There has been no kidney loss to rejection. Death-censored transplant kidney survival is no different than in our conventionally treated transplant recipients.

The HLA-matched protocol has been successfully employed in two international transplant centers and is in industry-sponsored multicenter trial. The HLA-mismatched protocol continues in development to achieve durable mixed chimerism, thought necessary to tolerance and allowance of immunosuppressive drug cessation in the setting of HLA-disparity.



# Tandem Donor Heart (HT) and Autologous Haematopoietic Stem Cell Transplantations (AHSCT) for Patients with Severe Cardiac AL Amyloidosis

**David Ma, Andrew Jabbour, Peter MacDonald and John Moore**

Behalf of Heart and BM Transplantation teams, St Vincent's Hospital Sydney, Australia

AL (Amyloid Light Chain) Amyloidosis is the commonest type of Amyloidosis. It is a monoclonal plasma cell dyscrasia characterised by tissue deposition of immunoglobulin fragments leading to tissue and organ damage, with an overall incidence of 10 per million. The median age at diagnosis is 65 with a male predilection. AHSCT with high dose melphalan following induction chemotherapy is the preferred treatment for fit patients with systemic AL Amyloidosis, however, this precludes patients with cardiac involvement. Patients with severe cardiac AL Amyloid have a dismal prognosis with a median survival of less than 6 months and thus novel treatments are needed. An emerging therapy for patients with cardiac AL Amyloid is sequential HT and AHSCT. The co-location of heart transplantation and BM transplantation facilities at St Vincent's Hospital Sydney has facilitated the implementation of our clinical trial for these patients which was commenced in 2016. The feasibility, safety and outcomes of this ongoing trial will be presented with reference to published data.

# Conditioning Regimen of Autologous Stem Cell Transplantation in Multiple Myeloma

**Je-Jung Lee**

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High dose chemotherapy followed by autologous stem cell transplantation (ASCT) is recommended as a standard consolidative therapy for transplant-eligible multiple myeloma (MM) patients. The most commonly used conditioning regimen for patients with MM is high-dose melphalan (200 mg/m<sup>2</sup>; MEL200). There are ongoing efforts to find a more effective conditioning regimen. Intravenous busulfan (BU) has been developed in 2003 and has characterized by low first pass-effect to the liver. It is expected to avoid fatal hepatotoxicity such as VOD. Korean multiple myeloma working party (KMMWP) has conducted a prospective, multicenter, phase 2 study evaluating the efficacy and toxicity of intravenous BU-MEL as a conditioning regimen for ASCT in patients with MM. A total of 99 patients with MM, enrolled between January 2013 and March 2016, received intravenous BU (9.6 mg/kg) and MEL (140 mg/m<sup>2</sup>) prior to ASCT. The overall response rate after ASCT was 94.0%, including 43.5% with a sCR/CR, 27.3% with VGPR, and 23.2% with PR. The frequent severe non-hematologic toxicity (grade 3-4) was infection (26.3%) and stomatitis (15.2%). Three patients (3.2%) developed VOD. No treatment-related mortality was observed. After median follow-up of 26.1 months, the median PFS was 27.2 months (range: 13.0-41.4) and median OS was not reached. In this study, conditioning regimen of intravenous BU-MEL was effective and tolerable. At this meeting, I will provide the Korean data of intravenous BU-MEL and other BU-conditioning regimens for ASCT in patients with MM.

# Role of HSCT for MM in the Era of Novel Agents

**Shuji Ozaki**

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Multiple myeloma (MM) is a plasma cell neoplasm characterized by the presence of monoclonal immunoglobulin in serum and/or urine and clinical symptoms related to the CRAB features and myeloma-defining events. MM is a clinically and cytogenetically heterogeneous disease and survival outcome varies considerably depending on the risk status of each patient. Patient-related factors include age and frailty, disease-related factors include clinical stage and cytogenetic abnormality, and treatment-related factors include the use of novel agents and autologous hematopoietic stem cell transplantation (HSCT). Until now, treatment strategy for MM has been evolving rapidly by the introduction of several new classes of agents such as proteasome inhibitors, immunomodulatory drugs (IMiDs), and monoclonal antibodies. These highly effective modalities have led to deeper and durable responses including minimal residual disease (MRD) negativity, which have resulted in improvement of progression-free survival (PFS) and overall survival (OS). Nevertheless, high-dose melphalan followed by HSCT has been considered as the standard of care for the most powerful consolidation therapy after induction therapy for young or transplant-eligible patients. Currently, three-drug combination therapy consisted of proteasome inhibitors, IMiDs, and dexamethasone has become the most widely used regimen for induction therapy before HSCT. Recent clinical studies have confirmed a continued role for upfront HSCT in transplant-eligible patients even in the era of novel agents. Most clinical trials have shown the significant effect on PFS prolongation by HSCT but an OS advantage was not that clear. Notably, induction therapy itself with novel agents can induce a similar degree of deep response in some patients, and there is a debate regarding the optimal timing of HSCT (upfront or delayed), especially in patients who achieved MRD negativity after induction therapy. Unfortunately, the majority of patients eventually relapse even after HSCT, and consolidation and maintenance approaches have been tested to maximize the benefit of HSCT. Among these trials, European studies have shown an OS advantage by tandem HSCT, especially for patients with high-risk cytogenetic abnormalities. For the purpose of long-term disease control, efficacy and feasibility of maintenance therapy have been evaluated extensively by using IMiDs, proteasome inhibitors, or monoclonal antibodies. A meta-analysis of clinical studies on lenalidomide maintenance has shown an OS advantage after HSCT. However, high-risk patients harboring t(4;14), t(14;16), or 17q- and those with ISS stage III did not seem to benefit from lenalidomide maintenance, and risk-defined treatment stratification needs to be further established. Thus, the management of MM is undergoing a major paradigm shift along with recent advances in understanding of pathogenesis and development of novel therapeutic drugs. The latest therapeutic strategies including HSCT and the future perspectives in the management of transplant-eligible MM will be discussed.

# Autologous Stem Cell Transplantation in Light Chain Amyloidosis

**Kihyun Kim**

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Light chain (AL) amyloidosis is clonal plasma cell disorder producing amyloidogenic proteins which deposit in various organs such as heart, kidney, gastrointestinal track and peripheral nerve, make organ dysfunction. As the clone is usually small, it often resulted in delayed diagnosis which makes this disease more complicated and fatal.

Although treatment direct to the amyloid deposit are under development, the mainstay of current treatment is to eradicate clonal plasma cells which produce amyloidogenic proteins. Most of the treatment came from the treatment of multiple myeloma (MM) which is the most common form of plasma cell disorder.

High dose chemotherapy with autologous stem cell transplantation (ASCT) induce high rate of hematologic response and organ response for prolonged duration. The morbidity and mortality of ASCT in AL amyloidosis are higher than those of MM and only small portion of the patients are indicated for ASCT. Randomized trial performed in France showed inferior survival due to the high mortality of high dose treatment group. However recent advances of supportive care and selection criteria have improved the mortality rate.

In this session I will review the recent improvement of ASCT in AL amyloidosis and present our experience in Korean patients.

# Role of Allogeneic Hematopoietic Stem Cell Transplantation for Multiple Myeloma

**Chiaki Nakaseko**

Department of Hematology International University of Health and Welfare School of Medicine, Japan

Multiple myeloma (MM) is an incurable clonal plasma cell hematologic malignancy and is usually a disease of the elderly and its' median age at diagnosis is 65 years. Modern therapy for MM includes corticosteroids, immune-modulatory drugs (IMiDs), proteasome inhibitors, and monoclonal antibodies. Besides, autologous hematopoietic stem cell transplantation (auto-HSCT) in combination with high-dose chemotherapy has been considered as a frontline strategy for younger MM patients. Although these therapies dramatically increased patients' response rate and survival rate, most patients could not maintain a sustained remission and relapse ultimately. Allogeneic HSCT (allo-HSCT) has been considered as a potential way to cure MM by graft-versus-myeloma (GVM) effect. However, allo-HSCT has not been widely used to treat MM patients due to high risk of treatment related mortality (TRM) and the occurrence of GVHD during several decades. To reduce the TRM, reduced-intensity conditioning (RIC) regimen has been mainly used rather than myeloablative conditioning (MAC) regimens. Seven prospective studies have compared the strategy of auto-HSCT followed by RIC allo-HSCT with tandem auto-HSCT. The TRM was higher in allo-HSCT arms and ranged from 5 to 16%. Five of the seven trials showed superior complete remission (CR) rates, and two studies showed significantly longer progression-free survival (PFS) and overall survival (OS) favoring allo-HSCT. The heterogeneity in patient eligibility, randomization, and conditioning regimens across these studies makes it difficult to draw definitive conclusions. In addition, the role of allo-HSCT still remains unclear in the novel agent era.

Between 2005 and 2017, 51,586 patients received the first allo-HSCT in Japan, including 302 patients with MM (5.9%). The 5-year OS of related bone marrow transplantation (BMT) (n=70) for MM was 29.0%, related peripheral blood stem cell transplantation (PBSCT) (n=128) was 27.6%, unrelated BMT (n=64) was 29.8% and unrelated cord blood transplantation (CBT) (n=40) was 8.0%, respectively. To further evaluate the efficacy of allo-HSCT for MM in the novel agent era, we conducted a retrospective study of 65 patients with MM who underwent allo-HSCT at 19 institutions in Japanese Society of Myeloma from 2009 to 2016. Patients received a median of 3 (range, 1 to 7) lines of prior therapy, including at least 1 novel agent, except for auto-HSCT. Of the 65 patients, 24 (16 HLA matched, 8 HLA mismatched), 2 (2 HLA matched), 33 (20 HLA matched, 13 HLA mismatched), and 6 patients received related PBSCT, related BMT, unrelated BMT, and unrelated CBT, respectively. Seventeen (26%) patients received MAC regimens, whereas the other 48 (74%) patients received RIC regimens. The 3-year PFS and OS rates were 18.8% (95% confidence interval [CI], 9.6% to 30.3%) and 47.2%

(95% CI, 33.9% to 59.4%), respectively. In a multivariate analysis, an age  $\geq 50$  years and less than a very good partial response (VGPR) before allo-HSCT were independent significant adverse factors for PFS (hazard ratio [HR], 2.30,  $P = .0063$ ; HR, 2.86;  $P = .0059$ ) and OS (HR, 2.37,  $P = .013$ ; and HR, 2.74;  $P = .040$ ). In contrast, the 3-year PFS and OS rates in patients  $< 50$  years of age who achieved a VGPR or better before allo-HSCT were 64.3% (95% CI, 29.8% to 85.1%) and 80.2% (95% CI, 40.3% to 94.8%), respectively. The overall response rate was 86.4% (95% CI, 75.0% to 94.0%). The proportion of VGPR or better increased from 29% before allo-HSCT to 71% after allo-HSCT. The non-relapse mortality at 3 years was 23.4% (95% CI, 13.8% to 34.4%). Only an age  $\geq 50$  years was associated with higher non-relapse mortality (HR, 4.71;  $P = .015$ ). These data showed that allo-HSCT is feasible for heavily pretreated patients with MM, even in the novel agent era. Allo-HSCT in particular is a promising therapy for young and chemo-sensitive patients.

Another way to improve the outcome of allo-HSCT might be to use an appropriate maintenance therapy after transplantation. Bortezomib has been shown to be efficacious at maintaining myeloma control after allo-HSCT without an increased risk of GVHD. On the other hand, IMiDs can stimulate T cell and natural killer cell immunity and may induce GVHD with or without GVM effect when used in the post-allo-HSCT setting. HOVON-76 trial prospectively enrolled 35 patients who underwent RIC allo-HSCT followed by lenalidomide 10 mg on days 1–21 of a 28-day schedule for a total of 24 cycles. After two cycles, an unexpectedly high number of patients (47%) had to stop treatment because of the development of acute GVHD. However, 37% of patients saw improvement in responses with an estimated 1-year PFS from the start of maintenance 69%. The investigators concluded that lenalidomide maintenance at 10 mg after allo-HSCT is not feasible due to induction of acute GVHD. In a later study conducted by the CIBMTR, relatively better tolerability, especially at lower doses, was observed. Thirty patients with high-risk myeloma undergoing RIC allo-HSCT were included. All the patients started therapy at lenalidomide 10 mg/day at a median of 96 days after allo-HSCT. Forty-seven percent of patients developed GVHD with the cumulative incidence of grades II–IV acute GVHD 3 months after starting lenalidomide of 30%. An overall response improvement of 33% was seen with lenalidomide maintenance. The PFS and OS at 18 months were 63 and 78%, respectively. Another phase I/II dose finding study of 24 patients concluded that 5 mg daily for 21 days followed by 1 week of rest given between day 100 and 180 after allo-HSCT is the maximum tolerated dose. A lower dose, starting near day 100, may produce encouraging results in high-risk MM patients.

In summary, allo-HCT, although a high-risk treatment modality, has the potential to provide long-term remission in a minority of high-risk patients and perhaps even cure some. Combining allo-HSCT with newer immunotherapies and novel agents is likely to further improve the clinical results. Which patients are ideal candidates for allo-HSCT is still an unanswered question, however, patients with high-risk MM, including those relapsing after novel agent-based therapy or early after auto-HSCT, who have responsive disease and good performance status should be evaluated for allo-HSCT, ideally through a well-designed clinical trial.

# Survey on the Cord Blood Banking Status in Asia-Pacific Nations -Harmonious Coexistence of Public and Family Cord Blood Banks-

**Young-Ho Lee**

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Cord blood (CB) has emerged as an alternative source of hematopoietic stem cells, and public CB banks (CBBs) have proliferated worldwide. Currently, more than 730,000 CB units are available worldwide, and around 35,000 CB transplantations have been performed. However, the introduction of new transplant protocols involving haploidentical family donors has led to a dramatic decrease in CB usage all over the world. In addition, serious threats to the family CBBs also include lower rates of utilization of stored CBs. However, there are also emerging opportunities for the industry, such as in the field of cell therapies and regenerative medicine. Besides public CBBs, networks of family CBBs are also commonplace to survive. These trends prompted us to investigate the current status of CBBs in Asia-Pacific nations and to establish the networking system for their CBBs whatever it is public or private.

With the friendly help from the APBMT secretariat, we obtained the data from the corresponding websites as well as email communications with the CBBs in 21 countries of the Asia-Pacific region.

In this survey, there have been 25 public CBBs in 12 countries, 35 family CBBs in 8 countries, and 17 hybrid CBBs in 6 countries. Identified inventory of 42 public CBBs including hybrid banks were 350,910 units with the released units of 23,896. Their utilization rates of stored CB units were from 0.3% to 70.4%. The informed cut-off cell dose for banking public CBs in most surveyed countries were 7-10X10<sup>8</sup> TNCs of post-processing. However, in this survey, only 35.7% (57,981/162,637) of stored CB units were >10X10<sup>8</sup> TNCs, with their range from 11.6% to 72.7%. Regarding family CBBs, 26 CBBs informed us their inventory of 922,121 units and 0.04% of utilization rate. Interestingly, several large companies (Global Cord Blood Group and VcanBio in China, Cordlife Group in Singapore+, LifeCell in India+) for family banking business have launched the hybrid type of CBBs in Asia-Pacific countries.

Repurposing the public CBB inventory would be needed to enhance CB use for hematopoietic stem cell transplantation as well as ongoing clinical trials in regenerative medicine and basic researches. In addition, public and family CBBs have to cooperate to make further breakthroughs in CB industry with the harmonious investigations in the clinical and basic researches using CBs, which could enhance the utilization rate of stored CBs in public and family banks.

# Expanding the Use of Publically Banked Cord Blood in Australia

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The BMDI Cord Blood Bank in Melbourne is one of three public cord blood banks in Australia, along with the Sydney Cord Blood Bank and the Queensland Cord Blood Bank at the Mater. Together these three banks comprise the AusCord Cord Blood Banks (CBB). All three banks are licensed by the Therapeutic Goods Administration (TGA) and hold international FACT-NetCord Accreditation. The AusCord CBB are funded by government and work closely with the Australian Bone Marrow Donor Registry for listing, search and release of CB for bone marrow transplants. There are more than 38,000 CB units searchable in the AusCord inventory and nearly 1,300 CB units have been released for transplant. Although CB will always be an important donor source for patients, the use of CB has declined in recent years for a variety of reasons. Strategies have been implemented across the AusCord CBB to ensure that the inventory continues to meet the needs of current donor selection practices. Some of these strategies include raising the minimum criteria for total nucleated cell count and CD34+ cell count of CB units processed and banked, and the use of next generation sequencing (NGS) for high resolution HLA tissue typing.

We also aim to expand the use of banked CB through the creation of clinical grade induced pluripotent stem cell (iPSC) lines from CB with homozygous HLA haplotypes common within the Australian population. It is planned that these stem cell lines will be available for clinical researchers or contract manufacturing organisations to derive their cells of interest for therapeutic use. To this end, we have established the methodology to create stable iPSC lines from small volumes of cryopreserved CB under GMP-compliant conditions. We have identified suitable CB donors within the BMDI Cord Blood Bank who have common homozygous HLA haplotypes. Ethics and government approval have been obtained to re-consent these donors in order to create and store GMP-compliant iPSC lines from a fraction of their banked CB. Success of this project will serve to expand the use of altruistically donated CB towards the development of many other types of cellular therapies.



# The Current Status of Cord Blood Banking and Transplantation in Vietnam

**Tran Trung Dung**

Head of Stem Cell Bank, Blood Transfusion Hematology Hospital, Ho Chi Minh City, Vietnam

In 1999, the first cord blood bank in Vietnam was established by Blood Transfusion Hematology Hospital, Ho Chi Minh City. So far, Vietnam has seven (07) cord blood banks nationwide, 03 hybrid banks (public and private combined) and 04 private banks, with total public inventory is estimated about 7,500 units.

There has been totally about nearly 50 cases of transplantation, mostly for pediatric patients with indications such as CML, ALL, AML, thalassemia,.... Particularly, a private hospital has used cord blood to transplant for some non-hematologic diseases such as: cerebral palsy, autism,...

Cord blood processing techniques are commonly using either by manual methods or by automatically processing systems (Sepax, AXN) depending on the policies of individual banks.

Cryopreservation devices is also optional, traditional tanks or fully automated system as BioArchives of Thermogenesis are chosen.

National standards and registry network have not been built yet. There are no CBUs shipment still now between domestic banks. The compliance of quality standards is different from each bank (AABB, Netcord, AsiaCord,...).

Our Cord Blood Bank – Blood Transfusion Hematology Hospital, in 2002, performed the first cord blood transplant in Vietnam and in 2004 became an official member of AsiaCord after being evaluated and accredited. Cord blood banking techniques and transplantation procedures are studied by our doctors and technicians from Cord Blood Bank-Tokyo-Japan. Quality standards for collection, processing, quality control testing and storage have been complying with the regulations of Netcord, FACT, Asiaticord. Fully automatic storage with BioArchives systems. Up to now, our inventory has been archived 6,170 units and 11 cases of transplant have been made since 2002, with diseases such as CML, ALL, AML, thalassemia.

Although in recent years, the number of cord blood transplants has generally decreased worldwide, however, we do hope that the trend of cord blood transplantation will develop again, especially when the limitations of cord blood grafting could be improved, with the combination cord blood with other stem cell sources, HSCs from cord blood expansion and multiple cord blood units using for transplantation. Therefore, the cooperation and standardization between the domestic and international banks in the region need to be established soon and co-operated more closely and effectively. Together linking between banks, allows to create a vast common inventory, will increase the ability to find matched units for transplant. Thereby, it will create a premise for the upcoming cooperation for other stem cell objects, such as: MSCs, iPS,...

# The Challenges and Future of Cord Blood Transplantation

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Cord blood (CB) is an alternative option of standard graft sources for hematopoietic stem cell transplantation (HCT), and has been increasingly used in adults with hematological malignancies. There is considerable evidence that CB is a promising option for patients who lack a human leukocyte antigen (HLA)-matched related or unrelated donor. Graft failure (GF) is a life-threatening complication of all kinds of HCT and occurs more frequently after CBT. Thus, to solve the problem of graft failure, we established a new conditioning protocol. Based on traditional myeloablative conditioning regimen (simplified as MAC) of Bu/Cy or TBI/Cy, Flu was added to Bu/Cy and CA to TBI/Cy for a modified myeloablative conditioning regimen (simplified as MMAC). For GVHD prophylaxis, ATG was omitted. To compare the prognosis of MMAC with MAC, we conducted a retrospective study including 58 patients who underwent CBT with MAC or MMAC from 2000 to 2011. Neutrophil and platelet engraftment rate, overall survival (OS) and disease free survival (DFS) were significantly higher in the MMAC group. Non-relapse mortality (NRM) was comparable ( $p=0.183$ ). To validate the outcomes noted in the MMAC group, we conducted a prospective single-arm clinical trial including 188 patients who underwent CBT with MMAC from 2011 to 2015. Engraftment rate, survival and NRM of the MMAC group in the prospective trial were similar to the MMAC group in the retrospective study. This study is the first to demonstrate the superiority of MMAC to MAC in CBT for hematological malignancies. However, delayed platelet engraftment (DPE) and platelet engraftment failure following UCBT remain common problems. To date, there is no standard therapy has been recommended. We designed a prospective randomized controlled trial with the purpose of determining whether recombinant human thrombopoietin (rHuTPO) improves platelet engraftment in patients undergoing single CBT. This trial enrolled 120 patients who suffered hematological malignancies between October 2016 and March 2018, and then underwent CBT in Department of Hematology, the First Affiliated Hospital of University of Science and Technology of China. A total of 60 patients were randomly assigned into the experimental group, in which they received rHuTPO on Day 14 after sUCBT with a dose of 300 U/kg once daily for a period of 14 days; the remaining 60 patients formed the control group. With a median follow-up of 336 days for the surviving patients, the cumulative incidence of PLT engraftment in the rHuTPO group was significantly higher than the control group ( $p=0.0294$ ). The median time of PLT recovery in the rHuTPO group was 43 days, which was significantly shorter than the control group ( $P=0.034$ ). The rHuTPO group also showed an advantage over the control group in infused PLT units (6 vs 8,  $p=0.0294$ ). Multivariate analysis confirmed the significance of differences in platelet engraftment between two groups. Here, we show that rHuTPO could significantly improve platelet engraftment and promote platelet recovery in patients with hematological malignancies who received UCBT; in the meantime, it could also effectively reduce the infusion of platelet.

# Cord Blood Transplantation for Advanced Hematological Malignancies in Japan

**Hisashi Yamamoto**

Toranomon Hospital, Japan

It was known that cord blood (CB) contains mainly T-cells with naïve phenotype, that HLA-mismatched CB grafts can safely be used as those of matched, and that CBT was accompanied by high rejection rate compared to the other donor-types. All these facts were translated into the notion that CB has only weak immunological potential. However, the initial conception of CBT has been changing dramatically based on recent results of basic research and clinical experiences, and CBT has now become one of the alternative stem cell sources for patients with a wide variety of hematological diseases.

Because CB confers the advantages of rapid and wide availability, CBT has been frequently performed in patients with advanced disease who need urgent transplantation. There was a concern regarding the capability of CB-derived lymphocytes to mediate sufficient graft-versus-leukemia (GVL) effects. However, the incidence of relapse after CBT is reportedly comparable to that after other stem cell sources. Several recent studies have shown even lower relapse rate in CBT compared to the others, despite a lower incidence of GVHD. We and others have reported a unique clinical manifestation termed pre-engraftment immune reactions (PIR), characterized by non-infectious high-grade fever, skin eruption, diarrhea, jaundice, and body weight gain early after CBT. The unique immune-mediated manifestation may have the potential to cause GVL effect from very early time point after CBT besides GVHD. Here we review the recent outcomes of CBT for advanced hematological malignancies and discuss the potential GVL effect of CB, focusing on PIR.

# A Progress of Stem Cell Transplantation in Thailand

**Suradej Hongeng**

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Hematopoietic stem cell transplant (HSCT) was established in Thailand since 1986. At present, there are 13 active center. A total number of transplanted cases is about 4000 cases. The recent annual number of transplants 400-450 cases. National Health Security Office (NHSO) reimburse for all patients with the certain criteria. Types of HSCT in Thailand include autologous transplant, allogeneic transplant including related, unrelated and haploidentical donors and also gene therapy especially thalassemia. Cellular therapy activities were consisted of NK and CAR CD19 cells. Sources of HSC are bone marrow, cord blood, and peripheral blood.

# Haematopoietic Stem Cell Transplant (HSCT) in Malaysia -An Overview

**Ng Soo Chin**

Subang Jaya Medical center, Malaysia

The first HSCT was performed at University Hospital, Kuala Lumpur for a Paediatric Acute lymphoblastic Leukaemia patient in 1987. Since then more HSCT centres are being set up in Malaysia and currently the busiest centre is Ampang Hospital follow by University Hospitals (UMMC and UKM) and also Subang Jaya Medical Centre -a private medical centre which contributed the third largest collection of both adult and Paediatric patients. Ampang Hospital has successfully increased the number of cases performed by setting up satellite HSCT centres at Penang and Johor General Hospitals.

The stem cell source was mainly (>90%) from peripheral blood (PBSC) while autologous HSCT has increased proportionately more than allogeneic cases. The overall causes of deaths were mainly due to underlying diseases (63%), sepsis (14%) and GVHD (8%). There was a discernible improvement of long-term survival of about 10% in the 2010-16 period of 67.5% as compared to 2005-2009 period of 57.4 %.

The challenges of providing adequate HSCT in a timely manner include funding, staff such as transplant physicians and nurses plus the supporting laboratory staff and physical facilities like HSCT and day-care wards and laboratory facilities. Newer HSCT techniques such as Haplo- identical transplant takes a long time to take off as the limitations mentioned above make introduction of new services a difficult task.

# Stem Cell Transplantation and Cellular Therapy in Iran

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Hematopoietic stem cell transplantation (HSCT) employing hematopoietic progenitor cells, either self (autologous HSCT) or donor-derived (allogeneic HSCT), is a potentially curative therapy for many hard-to-cure life-threatening diseases such as primary immunodeficiencies, inborn errors of metabolism, inherited erythrocyte disorders, bone marrow failure, hematologic malignancies and solid tumors. Iran has a 30-year background in HSCT. The first Iranian HSCT center was founded in 1989-1990. Over the past 3 decades, 16 other centers have been established in academic hospitals across the country, which institution of 10 of them occurred during the past 5 years, following the optimal expansion of basic and clinical stem cell-based knowledge. Hence, with 17 HSCT centers across the country, approximately 1,200 HSCTs are performed in Iran each year.

This figure is projected to increase because of the progress in the field of HSCT such as routine use of reduced-intensity conditioning regimens, introduction of alternative graft sources, recognition of newer indications for HSCT, launch of the Iranian National Stem Cell Donor Network (INSCDN), expansion of the number of Iranian donors, establishment of more HSCT centers and training of more HSCT experts via HSCT fellowship programs. At the same time, early and long-term HSCT outcomes continue to improve with enhanced patient and donor selection, upgraded techniques for hematopoietic progenitor isolation with higher purity, augmented transplantation protocols, and better preventive and supportive care.

In recent years and with the introduction of PhD fields in Iranian medical universities focused on developing novel cell- and tissue-based therapeutics, i.e. "Applied Cell Sciences" and "Tissue Engineering", new topics in clinical research on a variety of cellular therapies including adoptive cell transfer or immune cell-based therapy, gene therapy, and the repair of organ defects and damages using biological scaffolds, ex vivo cultured tissues and engineered organs have been rapidly developed. Currently, over 3000 basic and clinical scientists are working collaboratively to produce numerous products that are gradually receiving approval from the national food and drug agency. It is noteworthy that by 2019, the country has enjoyed and the public has profited by the approval of 5 cell- and tissue-based products.

**Keywords:** Hematopoietic Stem Cell Transplantation; Cell- and Tissue-Based Therapy; Refractory Diseases; Malignancies; Iran

# Challenges of Stem Cell Transplantation in Bone Marrow Failure Syndromes

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**Background:** Bone marrow failure syndromes are a diverse set of genetic & acquired disorders in which there is inability of the bone marrow to produce sufficient blood cells. There are different pathways discovered in BMF which can lead to cellular apoptosis and can predispose to malignant transformation. **Method:** The important disorders associated with Inherited Bone Marrow Failure Syndromes (IBMFS) are Fanconi Anaemia, Dyskeratosis Congenita, Shwachman-Diamond Syndrome, Diamond-Blackfan Anaemia and Congenital Dyserythropoietic Anaemia etc. The acquired bone marrow failure includes Aplastic Anaemia, PNH, Myelodysplastic Syndrome (MDS) and Acute Leukemia. A study was conducted on 386 patients underwent allogeneic stem cell transplants Armed Forces Bone Marrow Transplant Centre / National Institute of Blood & Marrow Transplant (AFBMTC/NIBMT) Rawalpindi - Pakistan. The selection of the patient, conditioning protocols and post-transplant management of these cases is done at AFBMTC/NIBMT. **Results:** Until now, we performed 353 allogeneic stem cell transplants (matched related) in Aplastic Anaemia. OS is 80.2% & DFS is 73.5%. 16 haploidentical transplants were done in Aplastic Anaemia and DFS is 62.5%. 33 allogeneic stem cell transplants were performed in IBMFS at Armed Forces Bone Marrow Transplant Centre, Rawalpindi. Out of these transplants, 27 patients were of Fanconi Anaemia and 06 kids of Diamond-Blackfan Anaemia. In Fanconi Anaemia, post transplant DFS/OS is 72.7% and TRM is 27.3%, while in Diamond Blackfan Anaemia DFS/OS is 100%. **Conclusion:** In bone marrow failure syndromes, Hemopoietic Stem Cell Transplantation (HSCT) is the only curative treatment but selection of the patient and refinement in conditioning and follow-up protocols are key to success.

**Keywords:** Inherited Bone Marrow Failure Syndromes, Fanconi Anaemia, Diamond-Blackfan Anaemia, Aplastic Anaemia

# The Current Status of HSCT in Mongolia

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In Mongolia, autologous hematopoietic SCT (HSCT) has been used to treat patients with hematological diseases since 2014. Since then, 18 patients have undergone with HSCT in our center, only center in the country. Of those, 45% are non-Hodgkin's lymphoma cases, 28% are multiple myeloma cases, 22% are Hodgkin's lymphoma cases and 5% is acute myeloid leukemia case. Stem cell source was from peripheral blood. Average count of the stem cell was  $4.54 \times 10^6$ . The conditioning regimens used were mainly myeloablative (BCNU based, high dose melphalan, Bu-Cy, Thio/Mel). Non-myeloablative regimens were bleomycin-based. The average age of patients was 38 years old. The main complication was infection such as para-proctitis and pneumonia. Those time, 3 patient was relapsed and took a salvage treatment. We faced 1 case of treatment related mortality.

We plan to do allogenic-HSCT in this year, and we are preparing for this project. Our major challenge is laboratory capacity.

Currently there is no unified national registry system in Mongolia. We intend to create cord blood bank and national registry.

In conclusion, autologous HSCT has been successfully adapted to routine clinical care in Mongolia.



# Bone Marrow Transplant in Nepal

**Bishesh Sharma Poudyal**

Civil Service Hospital, Nepal

Ever since the first bone marrow transplant (BMT) was performed in 2012, patients with blood disorders are not bound to travel to neighboring countries for BMT. Establishing a sustainable BMT program in a resource constraint setting and that too, in a government setup is a challenge. However, Civil Service Hospital is providing state of the art service for the last couple of years. Cost for autologous, allogenic and haploidentical bone marrow transplant is reasonably low compared to neighboring countries. Although BMT is only a curative option for patients with blood malignancies, benign blood disorders like thalassemia and aplastic anemia are highly curable with BMT and such patients should be offered BMT as early after diagnosis as possible. Because of low transplant cost and better outcome, Nepal can become a popular destination for medical tourism. This paper outlines the BMT activity in Nepal and describes, in some detail, the transplant program at Civil Service Hospital, Kathmandu, Nepal.

# Haemopoietic Stem Cell Transplantation in Myanmar: Experience on Non-Cryopreserved Autologous Stem Cell Transplantation for Myeloma

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**Background:** Being a developing country, Myanmar has initiated autologous hematopoietic stem cell transplantation (ASCT) only recently. Traditionally, ASCT requires cryopreservation of the stem cells before it is reinfused after high dose chemotherapy. However, there are several challenges to use cryopreservation in Myanmar including lack of trained technicians, financial constraints and irregular electricity with difficulty to maintain refrigerator temperature. Therefore, non-cryopreserved peripheral blood stem cells (PBSC) have been used at the North Okkalapa General and Teaching Hospital since the first transplant of Myanmar in 2014. This is the report of preliminary data on outcome of these cases and single center experience of this simple method which enabled us to perform successful autologous transplantation despite several limitations.

**Patients and Methods:** Patients with myeloma who achieved at least partial remission after minimum four courses of bortezomib based induction were offered autologous transplantation using PBSC. Mobilization was done with granulocyte colony stimulating factor (GCSF) alone or combined with chemotherapy until 2018 when mobilizing agent, plerixafor became available locally. Mobilized PBSC were collected by apheresis and stored at 4 degree Celsius in a pharmaceutical refrigerator without cryo-preservation. Once stem cell enumeration confirmed the count, high dose melphalan was given along with cryotherapy. Stem cells were reinfused within 24 hours after repeating CD34+ count and viability. Back-up generator was used to ensure stable refrigerator temperature for storage of PBSC before reinfusion. **Results:** From May 2014 to January, 2019, 13 myeloma patients including 3 relapsed cases in median age of 57 years (range 47 to 63 years) with male to female ratio of 1: 1.6, underwent ASCT. All were Durie-Salmon stage III with four having impaired renal

function and 11 were International Staging System (ISS) stage III. One had high-risk cytogenetics. Mobilization was performed with GCSF alone or with chemotherapy. In addition, 7 cases received plerixafor 20-24 mg. The dose of Melphalan ranged from 110-200mg/m<sup>2</sup> (median dose of 160.0 mg/m<sup>2</sup>). At an interval between 12 to 24 hours after melphalan, non-cryopreserved PBSC were reinfused at median CD34+ cells dose of  $3.30 \times 10^6$  cells/kg (range  $1.45-4.87 \times 10^6$  cells/kg) with rechecked viability above 90% in every case. Median engraftment time was 11 days (range 9-12) and 16 days (range 9-44) for neutrophils and platelets respectively. Oral mucositis was mild but grade II -III diarrhea was observed in 6 cases. There was no graft failure or mortality during first 100 days. Mean progression free survival was 19 months (range 4-48 months). During minimum follow-up of 6 months, relapse rate was 15.4 % (2 in 13) and non-relapse mortality was also 15.4% (2 in 13).

**Conclusion:** Using refrigerated stem cells without cryoprotectant made ASCT possible for myeloma patients from resource limited country even with the inexperienced hands of a new center.

**Keywords:** Non-cryopreserved peripheral blood stem cells, multiple myeloma, resource limitation

## Regenerative Clinic 21+ in Phnom Penh City, Medical Doctor and Founder, Cambodia

**Pheng Bora**

AABB, Cellular Therapy Certificate, Cambodia

Cambodia is one of the fast growing economic countries in South-East Asia.

Since Jan 2019, its National Cancer Center serves publics with nuclear medicine, radiation oncology, medical oncology, pediatric oncology and clinical hematology.

Particularly, for blood diseases, we experience (with quite successful results) in treating patients with MM, LNH, LH, ALL, AML and SAA using conventional protocol/chemotherapy. For example, SAA we successfully treated with horse ATG, AML (intermediate and low risk groups) were treated with 3+7 protocol without any deathly complications yet. We have most kind of hematology drugs, supporting items and more advance in diagnostic lab such as flow-cytometry. We also have platelet aphaeresis.

Due-to some challenges, Hematopoietic Stem Cell Transplant (HSCT) may can not be implemented in the NCC in the next several years. Since the HSCT can not be applicable in the territory, if there is cases, we send them to foreign countries and follow up with us after transplant.

## Haematopoietic Stem Cell Transplant Activity: Report from Sri Lanka

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Sri Lanka is an island country with a population of about 21 million. All patients in Sri Lanka are entitled to free medical care from any state hospital in the country. HSCT was however, commenced in the private sector in 2014 at Asiri Central hospital(ACH). The First National HSCT centre was established at National Cancer Institute, Sri Lanka(NCISL) and commissioned in 2016. This was due to a collaboration between the NCISL and National Blood Transfusion Service(NBTS) with St.Vincent's hospital, Sydney, Australia. This saw infrastructure development, mentorship, training and developing protocols culminating in the first successful autologous HSCT in December 2016. This report documents HSCT activity in 2018 and an update of the progress in Sri Lanka.

# Making HSCT Available for Every Filipino in Need: The Revival of HSCT Program at the National Kidney and Transplant Institute

**Lynn Bonifacio**

National Kidney and Transplant Institute, Philippines

One of the main reasons for the delayed progress of HSCT activity in the Philippines has always been inaccessibility due to the prohibitive cost and the limited number of transplant centers in the country. To address these, the HSCT program of the National Kidney and Transplant Institute (NKTi), was reestablished. HSCT was first performed in the Philippines at the NKTi in 1990. Since then, only 4 transplants were performed until 2002. In 2014, with the active support of the WBMT and the APBMT, the HSCT program in NKTi started anew and in 2018, construction of the HSCT Unit was completed. To date, a total of 8 patients have been successfully transplanted in the NKTi from the time the new HSCT unit opened in February 2019. The revival of the HSCT program in NKTi, a government-subsidized tertiary specialty center has made this life-saving treatment available to more Filipinos in need.

# Hematopoietic Stem Cell Transplantation in Indonesia

**Damani Santosa**

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Hematopoietic stem cell transplantation (HSCT) is standard treatment for several hematological neoplasms. Bone marrow transplant (BMT) performed in Indonesia (Semarang and Jakarta) since 1987, but stopped prematurely due to some unresolved problems. The hematopoietic stem cell source for BMT are bone marrow (BM), peripheral blood stem cell (PBSC), and umbilical cord blood (UCB). The hematopoietic stem cell can be infused through freshly or cryopreserved.

Dr. Kariadi hospital have been reorganized the BMT team and provide related services. We set up the BMT team, train the nurses and technicians, make the protocols and standard operation procedures, collaborate with the transplant centres and the international organizations that focus at BMT services.

Today our hospital have a BMT team, 10 positive pressure rooms with HEPA filter, apheresis unit, local protocols and standard operation procedures. The collaborations made with NUH Singapore and C2C foundation. Two nurses were trained by NUH as apheresis operator and BMT clinical nurse. One laboratory technician assigned to stem cell processing. Sixteen doctors and 37 nurses attended in training that organized by Dr. Kariadi Hospital in collaboration with the C2C foundation. The HLA examination was referred to Histogenetic laboratory. During 2018-2019 period, 5 patients were transplanted with autologous of preservation HSCT consist of 2 patients with AML, 3 patient with multiple myeloma.

**Keywords:** *autologous bone marrow transplant, BMT, AML, Multiple myeloma*

# Experience of Autologous and Allogeneic Stem Cell Transplantation in Bangladesh

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## Background:

The journey of autologous stem cell transplantation was started first in Bangladesh on March 2014 at the largest and leading tertiary care government hospital of country, Dhaka Medical College Hospital(DMCH) with joint collaboration between Massachusetts General Hospital(MGH),Boston USA and DMCH. Later three more centers eg. Apollo hospitals Dhaka and Combined Military Hospital ( CMH) started the transplant program by the year 2016 and BSMMU( Bangabandhu Sheikh Mujib Medical University) started on 2018. Recently DMCH and Dhaka CMH also started Allogeneic HSCT program at their transplant center. The purpose of this article is to describe the outcome of autologous stem cell transplanted patients for different hematological malignancies and to share the first ever experience of Allogeneic transplant in Bangladesh.

## Cases:

We retrospectively analyzed 70 post stem cell transplanted patients at different centers of Bangladesh from March 2014 to July 2019 .

## Result:

As of July 2019, the leading center DMCH performed 42 HSCT including one allogeneic HSCT followed by CMH Dhaka did 14 cases including one allogeneic, Apollo Hospitals Dhaka did 13 and BSMMU did 1 auto transplant.

Among this total 70 patients majority were ASCT/autologous stem cell transplanted (68) and only two were allogeneic stem cell transplant. Among 68 ASCT, Multiple Myeloma (MM)=27, relapsed/refractory non-Hodgkin Lymphoma(NHL) =19, relapsed/refractory Hodgkin Lymphoma =16 and relapsed Acute Myeloid Leukemia (AML) =05. The M:F ratio is about 4:1, average age 40 years( 16-71Y) for all cases. All the myeloma patients were conditioned with high dose melphalan (200 mg/m<sup>2</sup>) , lymphoma patients were with BEAM standard regimen and AML were with standard Bu-Cy. Average engraftment of neutrophil and platelet was D+9 and D+11 respectively for all patients. Major post-auto transplant complications were bacteremia(19), pneumonia (6), Clostridium difficile colitis(4), hemorrhagic cystitis (03), CMV cystitis (1) and PRES(1) those were managed successfully. Two year Progression Free Survival (PFS) is 70% over a median observation period of 36 months for patients in DMCH. The transplant related mortality (TRM) in first 100 days is nil (0%).

CMH, Dhaka performed one allogeneic HSCT in a 18 year male for AML from full HLA-matched sibling donor on October 2018 by reduced intensity conditioning regimen (Flu-Mel), engrafted within D+17 and following that patient is in remission till now. He had mucositis, bactremia, hemorrhagic cystitis during hospital stay and



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- 24<sup>th</sup> Annual Congress of APBMT  
- 24<sup>th</sup> Annual Congress of KSBMT  
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recovered well later on.

DMCH recently performed an allogeneic stem cell transplant in a 29 year female for relapsed Ph+ ALL from full HLA matched sibling donor on 3rd July 2019 by myeloablative Bu-Cy conditioning regimen. Patient had developed grade III-IV mucositis and Busulfan induced seizure. She engrafted on D+11.

**Conclusion:**

Establishing stem cell transplant unit was a challenge in developing country specially in government hospital and it was successfully done at Dhaka Medical College Hospital with the support of government and that also led the private hospitals to develop stem cell transplant program. Our goal is to continue transplant program in all established center with a vision to give best care service for hematological malignancies and also for thalassemia and aplastic anaemia.

# How to Study Human Immunology

**Eui-Cheol Shin**

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Recently, there is a growing interest in research techniques for studying the function of human T cells, as immuno-oncology studies have become popular. However, there are many difficulties in studying T cells in human patients. Mouse studies have largely addressed the difficulty of studying antigen-specific T cells with T cell receptor transgenic mice, but this method could not be applied to human studies. Recently, various techniques for studying human T cells have been developed to allow the direct *ex vivo* analysis of antigen-specific T cells obtained from patients. This lecture introduces recent advances in the study of human T cells and how they can be applied to human immunology studies.

# Multicolor Flow Cytometric Analysis of Human T cells

**Jong Hoon Kim**

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T cells play a role in adaptive immunity of our immune system. They protect our body from foreign antigens or contribute to the pathogenesis in various diseases. T cells contain many subtypes acting distinct roles with their own antigen specificity, and can be changed or differentiated depending on the environment. This nature of T cells sometimes makes their research difficult; however, researchers have overcome these problems after utilizing flow cytometric analysis. Especially, multiparameter flow cytometric analysis is useful for studying human T cells due to limited samples. Numerous T cell subsets can be identified through differential expression of cell surface markers. Intracellular and secreted cytokines can be measured in data from flow cytometry. Antigen-specific T cells are characterized by using multimer staining. Various data including cell signaling, telomere length, apoptosis, and the level of reactive oxygen species is also analyzed in individual cell level using flow cytometric technique. Recently, several programs have been introduced to visualize multiparametric data from flow cytometry. Collectively, multicolor flow cytometric technique is essential for studying the characteristics of human T cells.

# Haploidentical Transplantation with ex-vivo T-cell Depletion

**Rupert Handgretinger**

Children's University Hospital, University of Tuebingen, Germany

Haploidentical stem cell transplantation (HSCT) offers the chance for cure for almost every patient whose disease can be potentially cured by this approach. Especially in countries which have no unrelated donor registry or have no or only limited access to such registries, the use HLA-halfmatched donors (mainly parents, siblings or other relatives) allows transplantation without search for a HLA-matched donor and thus avoiding the risk of progression in malignant and also some non-malignant diseases during lengthy donor searches.

The main obstacle to haploidentical transplantation are donor-derived T-lymphocytes in the graft, which can cause severe and lethal acute and chronic Graft-versus-Host Disease (GvHD) especially in haploidentical HSCT. Therefore, various approaches have been introduced to deplete T-cells from the graft in vitro- For in vitro depletion, the TcR  $\alpha\beta$  depletion is currently widely used and has shown promising results in children and adults suffering from acute leukemias as well as from non-malignant diseases such as immunodeficiencies, hemoglobinopathies and others. This approach does not need post-transplant prophylactic immune suppression to avoid GvHD. In T-cell-depleted transplants, the immune reconstitution can be slow, thus exposing the patients at risk of mainly viral reactivations and infections.

Several new approaches have been introduced to overcome these obstacles. One is the use of donor-derived CD45RA-depleted lymphocytes to accelerate the immune recovery mainly in T-cell depleted transplants. This approach might have some risk of induction of GvHD depending on the number of infused T-cells, but has also shown promising results. Another approach is the use of donor-derived lymphocytes genetically modified to express an inducible caspase-9 suicide system as a safety switch. In case of GvHD, the T-cells can be rapidly eliminated in vivo by activation of the iCasp 9, which leads to apoptosis of the modified T-cells and very promising results have been reported using this approach in the setting of TcR $\alpha\beta$ -depleted grafts. Altogether, haploidentical transplantation using ex-vivo T-cell depletion is an evolving field and allows new strategies to improve the anti-malignancy effect of the grafts, to accelerate the immune recovery and to reduce the intensity of the conditioning regimen in selected patients.

# Haploidentical HSCT for Children and Adolescents with Hematologic Malignancy

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Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative treatment for children and adolescents with various malignant and non-malignant diseases. While human leukocyte antigen (HLA)-identical sibling donor is the preferred choice, matched unrelated volunteer donor is another realistic option for successful HSCT. Unfortunately, it is not always possible to find a HLA-matched donor for patients requiring HSCT, leading to a considerable number of deaths of patients without undergoing transplantation. Alternatively, allogeneic HSCT from haploidentical family members could provide donors for virtually all patients who need HSCT. Although the early attempts at allogeneic HSCT from haploidentical family donor were disappointing, recent advances in the effective *ex vivo* depletion of T cells or unmanipulated *in vivo* regulation of T cells, better supportive care, and optimal conditioning regimens have significantly improved the outcomes of haploidentical HSCT. The *ex vivo* techniques used to remove T cells have evolved from the selection of CD34<sup>+</sup> hematopoietic stem cell progenitors to the depletion of CD3<sup>+</sup> cells, and more recently to the depletion of  $\alpha\beta$ <sup>+</sup> T cells. The depletion of  $\alpha\beta$ <sup>+</sup> T cells produces grafts containing many  $\gamma\delta$ <sup>+</sup> lymphocytes and other effector cells including NK cells. While  $\alpha\beta$ <sup>+</sup> T cells are known to be associated with the initiation of GVHD,  $\gamma\delta$ <sup>+</sup> T cells can enhance immune reconstitution and are not implicated in GVHD. The  $\gamma\delta$ <sup>+</sup> T cells share characteristics of both the innate and adaptive immune system, displaying both innate cytotoxicity and antigen-presenting potential. These functional properties of  $\gamma\delta$  T cells make them a promising candidate for cancer immunotherapy. Unlike  $\alpha\beta$  T cells,  $\gamma\delta$  T cells are not MHC-dependent for antigen recognition leading to mediate GVL without GVHD. The recent emerging evidence for *ex vivo* T cell-depleted haploidentical HSCT has provided additional therapeutic options for pediatric patients with diseases curable by HSCT but has not found a suitable related or unrelated donor. The  $\alpha\beta$ <sup>+</sup> T cell depletion is the current approach applying in haploidentical HCT at our center and more than 150 cases of haploidentical HCT using  $\alpha\beta$ <sup>+</sup> T cell-depleted grafts have been performed so far.

In this presentation, I will to talk about the recent progress in haploidentical HCT and introduce our experience with transplantation using *ex vivo*  $\alpha\beta$  T cell-depleted technique for children and adolescents with hematologic malignancies.

# Recognition of Germline Predisposition Syndromes through A Genomics Approach for Patients with Hematologic Malignancies

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The 2016 World Health Organization classification incorporated several genes with somatic mutations and introduced a category for the germ-line predisposition syndromes in myeloid neoplasms. As the need for multiple gene testing has increased, we have designed a comprehensive next-generation sequencing (NGS) assay comprising 215 genes to detect somatic mutations, translocations, and germ-line mutations and have evaluated its clinical utility in patients with myeloid neoplasms. In addition to putative somatic mutations, we found that 8.4-11.6% of patients with acute myeloid leukemia and 12.9% of patients with myeloproliferative neoplasms were thought to have germ-line mutations, and most were heterozygous carriers for autosomal recessive marrow failure syndromes. We also performed whole exome sequencing and gene panel testing in another cohort for 139 patients with acute myeloid leukemia and found germline predisposition gene mutation was identified in 16 patient (16/180, 8.9%) including 10 adults and six children. Patients harboring germline mutations tended to have earlier onset of disease ( $P=0.006$ ), and to have smaller number of accompanied somatic mutations ( $P=0.024$ ). In summary, germ-line predisposition mutation is not uncommon in patients with myeloid neoplasms and consideration on biology and clinical aspect of the mutations should be made in this disease category.

# Novel Pathways to Leukemia Predisposition – Challenges for Haematopoietic Stem Cell Transplantation

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## Introduction

Haematopoietic Stem Cell Transplantation (HSCT) is a potentially curative therapy for haematological malignancies (HM). Numerous factors need consideration to ensure optimal outcomes including options of matched related or matched unrelated donors, age of patient and donor, and co-morbidities. Despite optimising for donor selection, conditioning and GVHD prophylaxis, the morbidity and mortality rates are high. Potential mechanisms for variability in outcome remain unknown.

Over the last 20 years, it has become clear that there are genetic factors that contribute significantly to the development of HM. Most well characterised are genes that predispose to myeloid malignancies in a autosomal dominant manner, including *RUNX1*, *CEBPA*, *GATA2*, *DDX41*, *SAMD9*, *SAMD9L*, *ETV6*, *TERT*, *TERC*, *ANKRD26*, *ACD*, *SRP72* and Chr14q duplication. Of note, *RUNX1* and *ETV6* as well as *PAX5*, *IKZF1* and *TP53* also predispose to lymphoid malignancies. There are increasing numbers of cases being reported demonstrating poor outcome following allogeneic stem cell transplant from siblings carrying predisposing mutations. Hence, it is important where possible to screen donor siblings or family members with suspected or known familial predisposition to avoid transplantation of predisposed bone marrow cells.

Further, we and others have seen recipients receiving donor-derived leukaemia or donor-derived clonal haematopoiesis of indeterminate potential (CHIP) both with poor outcomes. Older patients tend to have older donors, which is associated with poor outcome compared to younger matched unrelated donors, most probably due to clonal haematopoiesis in older sibling donors. These findings suggest a need for screening of donors for pathogenic predisposing or acquired mutations, and many places are now moving towards this routinely. Predisposition may also be multigenic with the rate of penetrance or age of onset due to 2 or more

contributing pathogenic variants. In these cases, it may be difficult to predict outcomes if one or more of these variants is not present.

Many places world-wide have adopted American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) guidelines for classification of the pathogenicity of genetic variants for help with clinical decision-making. This is a very useful tool, but challenges occur with variants of unknown significance (VUS), and whether these should be considered in donor selection within families.

Evidence is growing for the role of DNA damage repair pathway gene mutations (e.g. in *BRCA1*, *BRCA2*, *PALB2*) not only in predisposition to solid cancers but also blood cancers. Their role in post-HSCT outcomes is not clear. We also have evidence that pathogenic variants in Fanconi anaemia genes may predispose to therapy-related myeloid malignancy (i.e. t-MDS or t-AML following treatment of other primary cancers) with very poor outcome. This may predicate the use of genetic screening to identify at risk individuals with, for instance, non-Hodgkin lymphoma that would benefit from immediate HSCT (with associated risks) rather than the current recommended chemotherapy regime.

Our understanding of leukaemogenic processes continues to improve, and may shed light on why some HSCT recipients do well and others very poorly. Knowledge of inherited variants can already help with donor selection and, in the future, for choice of pre-HSCT conditioning strategies and treatment options for patients with HM.



# Designing an Optimum Conditioning Regimen for Malignant Disease

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# Novel Attempts to Improve Conditioning for Malignant Disease

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Attempts to improve the conditioning prior to hematopoietic cell transplantation (HCT) for acute leukemia may include 1) utilizing a different combination of well-established chemotherapeutic agents, 2) implementing a reduced intensity conditioning (RIC) regimen to allow for HCT in elderly patients or patients with comorbidities, and 3) incorporating novel drugs into conditioning.

Established myeloablative conditioning (MAC) regimens for acute leukemia include the combinations of total body irradiation (TBI) and cyclophosphamide (Cy), busulfan (Bu) and Cy, or Bu and fludarabine (Flu). Different formulations of such MAC conditioning, such as TB/Bu/Flu and the addition of idarubicin to TBI/Cy, have been used in patients with high risk acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL).

A RIC regimen may be attempted in patients who are likely to experience significant toxicity with a MAC-based transplant. Reported RIC regimens include Bu/Flu with a lower cumulative dose of Bu administered compared to a MAC regimen, and Flu/melphalan combination. Studies have shown similar post-transplant outcomes between patients who received MAC and RIC-based HCT, although the greater risk of disease relapse after RIC remains a major concern.

Chemotherapeutic agents with a relatively short history as part of conditioning for hematological malignancies include treosulfan and clofarabine. Treosulfan is an alkylating agent with significant anti-leukemic and immunosuppressive properties, and limited extramedullary toxicity. Clofarabine is a purine nucleoside anti-metabolite that has been reported as part of RIC-based HCT for acute leukemia. Further studies are necessary to clarify the potential advantages of these novel drugs.

Overall, the key components of each institution's conditioning regimen for hematological malignancies are based on institutional experience and preference, and may not be amenable to significant change. However, conditioning for more exceptional cases, such as that prior to HCT for primary refractory leukemia or the conditioning of a second allogeneic HCT, may benefit from the redesigning of chemotherapeutic combinations, adjustment of conditioning intensity, and the introduction of novel agents to optimize patient outcome after transplant.

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# The Role of the Intestinal Microbiome in Allogeneic Hematopoietic Cell Transplantation

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Relationships between microbiota composition and clinical outcomes of patients following allogeneic hematopoietic cell transplantation (allo-HCT) have been described in single-center studies. Geographic variations in the composition of human microbial communities and differences in clinical practices across institutions raise the question of whether these associations are generalizable.

Therefore, we studied 8,767 fecal samples from 1,362 allo-HCT patients at four centers on three continents by 16S ribosomal sequencing. In an observational study, we examined associations between microbiota diversity and overall survival during two years of follow-up after allo-HCT with proportional-hazards analysis. We observed reproducible patterns of microbiota disruption characterized by loss of diversity and domination by single taxa. Low diversity in the peri-neutrophil engraftment period was reproducibly associated with increased risk of death (multivariate-adjusted HR 0.48, 95% CI 0.30-0.77,  $p = 0.002$  in the largest cohort). Subset analysis suggested that these reductions in overall survival were in part due to an increased risk of transplant-related mortality and graft-vs-host disease. Baseline pre-HCT samples already bore evidence of microbiome disruption, and low diversity prior to transplantation was associated with poor survival.

In addition, we found that *Enterococcus faecium* dominates the intestinal microbiota of up to 65% allo-HCT patients early after transplant at all four transplant centers. Enterococcus domination was associated with an increased incidence of acute graft-versus-host disease (GVHD), increased GVHD-related mortality, and reduced overall survival. Post-transplant expansion of Enterococci was also observed in mouse models of GVHD in the absence of antibiotic treatment. Spiking a minimal flora with Enterococci in gnotobiotic mice exacerbated lethal GVHD. Metagenomic sequencing of human and murine Enterococcus-dominated fecal samples revealed an enrichment of lactose and galactose degradation genes, a pathway necessary for Enterococcus growth in vitro. A lactose-free chow attenuated the intestinal outgrowth of Enterococcus and reduced the severity of lethal GVHD in mice. In patients, a lactose-non-absorber genotype was associated with an increased Enterococcus abundance after cessation of antibiotic treatment after allo-HCT.

In conclusion, the concordance of microbiota disruption patterns and their associations with clinical outcomes suggests that approaches to manipulate the intestinal microbiota with the aim of improving allo-HCT clinical outcomes may be generalizable.

# FMT for Refractory GVHD

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The gut microbiota provides an intestinal biological barrier against pathogens and has a pivotal role in the maintenance of intestinal homeostasis and the modulation of the host immune system. The specific changes in the composition of gut microbiota, termed dysbiosis, have been associated with various diseases, including *Clostridium difficile* infection (CDI), inflammatory bowel disease, irritable bowel syndrome, metabolic syndrome, obesity, type I and II diabetes, atopy, multiple sclerosis, autism, colorectal cancer, etc. Restoring a healthy microbial community is therefore a promising therapeutic strategy for diseases related with gut dysbiosis. Fecal microbiota transplantations (FMTs) are increasingly being performed in clinical practice to restore the physiological composition of the gut microbiota. FMT has become a standard treatment for recurrent CDI and it is associated with a cure rate of >90%.

The role of the gut microbiota and its potential influence on clinical outcomes for patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HCT) has been investigated in recent years. Allo-HCT leads to dysbiosis and disruption of intestinal homeostasis as a result of the conditioning regimen, use of broad-spectrum antibiotics, alterations in nutrition, and donor cell-derived immune reconstitution. Analyses of fecal specimens taken from recipients of allo-HCT around the time of engraftment have shown that reduced intestinal microbiome diversity is associated with significantly worse survival outcomes such as acute graft-versus-host disease (GVHD) and disease relapse. Based on these recent advances in the field, several interventional studies are ongoing that will alter microbiota by means of diet and prebiotics, antibiotics, probiotics, microbial metabolites, and FMT. Although the evidence to support the effectiveness of FMT in treating GVHD is very limited and to this date is comprised of only case series, preliminary reports and studies of FMT in allo-HCT recipients suggest that it is safe, feasible, and associated with promising efficacy in multiple clinical settings. However, there are many unanswered questions regarding FMT, including identification of the best FMT donors, appropriate donor screening before FMT in immunocompromised patients, long-term safety, and regulatory issues. In addition, more research is needed to elucidate the multiple mechanisms by which FMT can reset the intestinal microenvironment after allo-HCT and to provide clarity regarding the appropriate clinical indications for FMT in this specific population.

# Selection between Autologous or Allogeneic Transplantation as First Salvage Consolidation in Relapsed/Refractory T- and NK/T-Cell Lymphomas

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Mature T- and natural killer (NK)-cell lymphoma (T-NHL) comprise a large spectrum of lymphoproliferative disorders with widely differing geographic distribution as well as distinct morphological, pathophysiological, molecular, and clinical characteristics. With increasing knowledge of their immunophenotypic and molecular characteristics T-NHL have repeatedly been reclassified, mirroring important progress in basic science, detection of new risk factors, the description of new potential therapeutic targets, and their therapeutic exploitation. Despite much progress, the prognosis for T-NHL is still poor for several reasons. First, anti-CD20 antibody, such as rituximab, has not been introduced in primary therapies, and CHOP, which has been used for decades, is currently being used as a standard therapy. Second, the salvage chemotherapeutic drugs used for recurrent B-cell lymphoma have also been applied for the treatment of refractory T-NHL. For patients with relapsed or refractory T-NHL, investigational drugs such as pralatrexate, romidepsin, belinostat, alisertib, lenalidomide, or mogamulizumab have been actively studied. Disappointingly, the effectiveness of the new drugs was limited and the duration of the response was short. Third, T-NHL contains several subtypes related to the latent viral infection which show resistance to anthracycline-based chemotherapy and poor therapeutic outcomes. In order to improve the treatment outcome, it seems necessary to develop new anti-cancer drugs as well as effective anti-viral drugs. Fourth, there is a lack of good clinical guidelines for the treatment of T-cell lymphoma. Although the incidence of T-NHL is slightly higher in Asia than in the West, the absolute number of T-NHL patients is very low and therefore it seems to be difficult to perform randomized clinical trials. Fifth, T-NHL does not show any promising targets of expressing surface or intracellular signaling molecules. Unlike B-NHL, T-NHL does not have a strong game changer such as anti-CD19 CAR-T cell therapy. Combinations with the anti-CD52 antibody alemtuzumab and CHOP (A-CHOP) in T-NHL did not show survival improvement because of serious infectious complications. Sixth, although treatment guidelines for T-NHL include autologous stem cell transplantation (ASCT) as a treatment option for patients in the first CR or PR, the role of ASCT in relapsed/refractory T-NHL is unclear. In fact, it is very difficult to reach remission status with salvage treatment in these patients before transplantation. Some patients who do proceed to receive ASCT is limited to a small number, and the long-term survival rate of ASCT is still poor. Seventh, a retrospective study of allogeneic stem cell transplantation (SCT) in relapsed/refractory T-NHL patients demonstrated PFS and OS rates of 40% and 50% at 5 years, respectively and high treatment-related mortality rates (around 30%) associated with the use of standard-intensity conditioning have been attributed primarily to the advanced age

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of patients with relapsed/refractory PTCL. Recently, allogeneic SCT using haploidentical donor and reduced-intensity conditioning regimen has been actively performed and clinical experience and outcome have been improved in real clinical practice. Taken together, both autologous and allogeneic SCT play an important role to induce a long-term survival in relapsed or refractory T-NHL unless effective new drugs are developed. In conclusion, currently allogeneic SCT seems to be more likely to develop successful survival outcome than ASCT in relapsed or refractory T-NHL

# Optimizing the Transplant Strategies in Relapsed/Refractory Hodgkin Lymphoma in the Era of New Agents

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Hodgkin lymphoma (HL) is highly responsive to conventional chemotherapy (CT). Close to 90 % of patients even with advanced disease are cured with modern CT sometimes followed by irradiation. Patients who prove refractory to or relapse after first-line therapy, do significantly worse. High-dose therapy (HDT) followed by autologous stem cell transplantation (auto-HCT) is the standard of care for medically fit patients with relapsed HL. The rationale behind considering auto-HCT as the standard of care for those patients with primary refractory / relapsed disease relies on the existence of two prospective randomized clinical trial where conventional salvage chemotherapy was compared to conventional salvage chemotherapy and consolidation with auto-HCT. In both studies, those patients that were consolidated with auto-HCT enjoyed better progression free survival (PFS) / time to treatment failure (TTF) than those patients that received salvage chemotherapy alone. The results of auto-HCT, however, vary significantly depending on a number of prognostic factors – the most important of which are the time interval between first-line treatment and relapse, the clinical stage at relapse, and the sensitivity of the tumor to salvage CT. More recently, the capacity to achieve a positron emission tomography (PET)-negative complete remission (CR) with the salvage regimen has also been demonstrated to be a good prognostic factor. For example, approximately 70 % of patients with late first relapse can be salvaged by auto-HCT, whereas not more than 40 % of patients suffering from early first relapse are rescued by this modality. There are different salvage protocols that can be used to achieve a second CR / chemosensitive disease status before taking the patient into the auto-HCT procedure. There is no demonstration that any of these strategies is better than the other one; effectiveness is quite similar between one and the other and the major difference is being seen in the toxicity profile of the different protocols. The other factor that has modified and probably will modify outcome after auto-HCT has been the introduction of brentuximab vedotin (BV), an anti-CD30 monoclonal antibody which is linked to monomethyl auristatine A. BV single drug was approved several years ago as single drug to be used in those patients that had already failed at least two prior lines of therapy and that were not considered candidates to be treated with auto-HCT. In addition to that, there have several prospective clinical trials that have looked into the combination of BV and several chemotherapy strategies (bendamustine, ICE, ESHAP; DHAP ...) with the objective to increase the percentage of patients achieving a metabolic CR and thus, to improve the final results of auto-HCT. BV single drug has also demonstrated efficacy as consolidation therapy (being given from day +30 to +45, at a dose of



1.8 mg/kg iv every 3 weeks up to 16 cycles) in those patients that are candidates for auto-HCT but that have high risk of relapse after the autologous procedure (primary refractory patients, relapsing patients with a short first CR and those with late relapses and extranodal disease at relapse). Because of all these modifications, we will probably see better results in the autologous stem cell transplantation setting in the near future.

In spite of the fact that auto-HCT is the standard of care for those primary refractory / relapsing patients, around 50% of them relapse after the procedure. The long -term outcome of these patients is dismal and they constitute a big unmet medical need. Allogeneic hematopoietic stem cell transplantation (allo-HCT) has been for many years the only curative treatment strategy for those patients relapsing / progressing after auto-HCT. The introduction of reduced intensity conditioning regimens back in the mid nineties was able to significantly reduce the high non-relapse mortality (NRM) observed with the use of myeloablative protocols in this setting and made allo-HCT available for the elderly and frail population of patients. Relapse rate, nevertheless, has always been the most important cause of treatment failure. Results of allotransplantation have improved over time and the introduction of cyclophosphamide post-transplant in the haploidentical donor setting has made allo-HCT a potential option for almost all patients being considered candidates for the procedure. Nevertheless, we also have the possibility to use "new" drugs in this setting. BV demonstrated the capacity to obtain 34% of metabolic CR when used as a single drug in patients relapsing / progressing after auto-HCT. The 5 years follow up of the pivotal phase II prospective clinical trial demonstrates that almost 20% of the patients were alive and disease free after being treated with the drug, raising the concept of BV potentially curing a small proportion of patients. More recently, check point inhibitors have also demonstrated to be very effective in patients relapsing not only after auto-HCT but also after BV. Both nivolumab and pembrolizumab are associated to a 20% metabolic CR in this population of patients and to a 40-45% partial remissions, with a very good safety profile. Because of the efficacy of these drugs, the best candidate for allo-HCT is nowadays less clear; one may want to still consider allogeneic transplant in a young and fit patient with an adequate donor and very high risk disease while new drugs might be considered a better option for those more elderly patients, with comorbidities and a no so aggressive disease. Finally, both types of strategies have been combined with the objective to try to give the best potential treatment option to these high risk patients; the use of BV before or after allo-HCT does not seem to offer specific complications to the patients. This is not exactly the case when we consider the combination of checkpoint inhibitors and allo-HCT. There are some evidences basically coming from small retrospective analysis that indicate that the administration of checkpoint inhibitors before or after allo-HCT, while leading to an excellent treatment combination in terms of efficacy, seem to be associated to an increased risk of transplant related toxicities (acute graft versus host disease, hiperacute febrile syndrome ...).

In summary, the role and results of hematopoietic stem cell transplantation is changing in patients with relapsed / refractory HL because of the introduction of new drugs.

# HSCT in Immune Dysregulation Syndromes: When and How?

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Primary immune dysregulation disorders (PIRD) are being increasingly recognized in clinical immunology and hematology-oncology practice. Several of these disorders present with either organ-specific autoimmunity (e.g., autoimmune cytopenia, autoimmune enteropathy, autoimmune endocrinopathy), lymphoproliferation, or hyper inflammation as prominent presenting manifestations. A significant proportion of these patients have an associated component of immune deficiency at presentation or develop immune deficiency over time. Immune deficiencies in this patient could range from mild hypogammaglobulinemia to combined immune deficiency with T-cell defect. Defects associated with PIRD affect regulatory T cell (Treg) number and function and critical signaling pathways in T cells. Moreover, many of these defects are also associated with perturbations in B cell homeostasis, including B cell survival and tolerance.

In addition to the classical disorders such as autoimmune lymphoproliferative syndrome (ALPS), immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome and common variable immune deficiency (CVID), several other immune regulatory disorders mimic these phenotypes. With the increasing use of genetic studies, monogenic causes of immune dysregulation affecting genes such as CTLA4, LRBA, STAT1, STAT3, PI3KD have been identified. Identifying these disorders at a genetic and immunophenotyping level is critical for long-term management. Several targeted therapies are currently available for many of the monogenic causes of immune regulatory disorders. Additionally, appreciation of underlying immune and genetic basis could facilitate the use of HSCT as a potentially curative strategy for these disorders.

Due to significant comorbidities and long-term complications associated with these disorders, early hematopoietic stem cell transplant is being advocated. HSCT outcomes have improved for several classical primary immune deficiency disorders such as severe combined immune deficiency and chronic granulomatous disease. However, HSCT outcomes for several of these monogenetic PIRDs, though is improving, is still suboptimal.

PIRD patients present several unique challenges pre-and post-transplant starting from who and when to consider HSCT in PIRD. Optimal disease control utilizing the best biological agent before HSCT, donor selection, selection of the conditioning regimen with particular consideration for the degree of immune ablation and myeloablation are some of the pre-HSCT considerations. Unique challenges post-transplant include a higher incidence of graft rejection, mixed chimerism, GVHD, autoimmune complications, infectious complications, and differentiating gut GVHD from primary pre-existing enteropathy. Additionally, some of these defects have a non-hematopoietic stromal component that may not be corrected post-HSCT.

# Unanswered Questions of HSCT for Primary Immunodeficiency

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Scientific Session 7

Primary immunodeficiencies (PIDs) are a heterogeneous group of rare genetic disorders of the immune system, and patients with PIDs are vulnerable to life-threatening infections, which can be fatal unless treated. Allogeneic hematopoietic stem cell transplantation (HSCT) has led to a great improvement in their survival since its first success with a boy with SCID. Now, a greater proportion of PIDs patients are able to receive HCT than the past along with a lot of technical improvements in the field of HCT including more optimized conditioning regimens, a better HLA-matching with an unrelated donor, fine stem cell manipulation methods, and a better supportive care. Nonetheless, a significant number of patients are still vulnerable to transplant-related morbidity and mortality, which makes it difficult in certain circumstances for a clinician to decide 'transplant or not'.

Gene therapy has become another realistic curative option for a subset of patients with PIDs. Based on the positive and promising safety and efficacy data collected since the first pilot studies of gene therapy for ADA-SCID patients in the early 1990s, "autologous CD34+ enriched cell fraction containing CD34+ cells transduced with a gamma-RV encoding for the human ADA cDNA sequence" was approved for licensure by the European Medicines Agency in May 2016. However, a current limitation of gene therapy is represented by its present availability in only few centers worldwide.

For the time being, HSCT will serve as a first-line option for a definite cure of selected subgroups of PIDs especially when a patient has a matched sibling donor. In SCID, the most severe type of PIDs, a matched sibling donor transplant can give rise to full immune reconstitution even without any conditioning when it comes to X-linked SCID.

In my talk, I'm going to show you my data on using very small volume of bone marrow cells obtained from HLA-matched which led to successful immune reconstitution in patients with X-SCID.

# Genome Editing using CRISPR

Hyongbum Henry Kim

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Cas9 and Cpf1 is an effector endonuclease of the class 2 CRISPR–Cas gene editing system. We developed a method for evaluating Cas9 and Cpf1 activity, based on target sequence composition in mammalian cells, in a high-throughput manner. A library of >11,000 target sequence and guide RNA pairs was delivered into human cells using lentiviral vectors. Subsequent delivery of Cas9 and Cpf1 into this cell library induced insertions and deletions (indels) at the integrated synthetic target sequences, which allowed en masse evaluation of Cas9 and Cpf1 activity by using deep sequencing. We defined target-sequence-dependent activity profiles of AsCpf1 and SpCas9 (Cas9 from *Streptococcus pyogenes*). Indel frequencies for 15,000 target sequences were used in a deep-learning framework based on a convolutional neural network to train Seq-deepCpf1. We then incorporated chromatin accessibility information to create the better-performing DeepCpf1 algorithm for cell lines for which such information is available and show that both algorithms outperform previous machine learning algorithms on our own and published data sets. Furthermore, by deep learning training on the large-scale activity data, we developed a computational model, named DeepCas9, that predict the SpCas9 activity with unprecedentedly high accuracy.

# Clinical Application of CRISPR-Cas System

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The bacteria-derived clustered regularly interspaced short palindromic repeat (CRISPR)–Cas system (such as Cas9 and Cpf1) is a powerful tool for genome engineering, and its programmability and simplicity have enabled various types of gene manipulation such as gene disruption, transcriptional and epigenetic perturbation, and targeted base editing. We focus on the development and clinical application of genome editing technology. Recently, we have applied CRISPR-Cas9 system for functional analysis of BRCA1 variants. Genetic mutations in BRCA1, crucial for the process of DNA repair and maintaining genomic integrity, are known to confer highly elevated risk of breast and ovarian cancers. Clinical genetic testing identified new BRCA1 variants, however, their functional assessment and identification of pathogenicity are challenges for clinical management. Using CRISPR-Cas9 based Base Editor, we identified several loss-of-function variants in BRCA1 which are classified as variants of uncertain significance (VUSs).

# Treatment Algorithm for Children with Severe Aplastic Anemia

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Over the past three decades, bone marrow transplantation (BMT) from a matched related donor (MRD) has been the treatment of choice for children with acquired severe aplastic anemia (SAA), and a majority of studies evaluating this treatment have shown overall survival (OS) rates exceeding 90%. Immunosuppressive therapy (IST) using antithymocyte globulin (ATG) and cyclosporine has been considered as the first-line therapy for children who lack a MRD. Horse ATG has been withdrawn from the market in the Asian countries and replaced with rabbit ATG. However, the optimal dose for rabbit ATG has not been established. Recent prospective randomized trial conducted

by Aplastic Anemia Working Party of the Asia-Pacific Blood and Marrow Transplantation Group revealed no significant difference in the efficacy and safety between the 2.5mg/kg and 3.5mg/kg doses of rabbit ATG. Up to now, no clinical studies have investigated the relationship between plasma rabbit ATG level and response to IST. Our data indicated interindividual variety in plasma ATG levels. Higher ATG level resulted in improved response rate to IST. Individualized dosing of ATG via a pharmacokinetic model may improve the response rate to IST and reduce the number of patients who require allogeneic stem cell transplantation following IST.

A recent European Group for Blood and Marrow Transplantation (EBMT) study of patients aged <20 years who were initially treated with hematopoietic stem cell transplantation (HSCT) from either a MRD or a matched unrelated donor (MUD) showed comparable 2-year failure free survival (FFS) rates which were far superior to the 2-year FFS rate resulting from IST. Importantly, the outcome after upfront HSCT from a MUD was better than that after HSCT from a MUD performed as rescue after a failed response to IST. In Japan, we also found excellent outcomes after upfront BMT from a MUD in a retrospective study of 33 children with AA. On the basis of these results, upfront BMT from a MUD for children with SAA can be selected if a suitable MUD will be found quickly.

Early studies demonstrated that the use of unrelated cord blood transplantation (UCBT) for severe AA was associated with a higher incidence of graft failure and poor outcome. However,

we recently reanalyzed the outcome of AA children who received UCBT and found that overall survival (OS) has dramatically improved. The 5-year OS was 94% in 17 children who received UCBT after 2006. Unexpectedly, our study revealed that the ATG regimen was an unfavorable factor for survival. Only 1 of 12 patients died in the non-ATG group, but 7 of 15 patients died in the ATG group. Our study suggests that fludarabine+ cyclophosphamide/melphalan+ low dose total body irradiation without ATG is potentially an optimal conditioning regimen for UCBT.

Another alternative choice is haploidentical (HID)-HSCT. According to the latest recommendations of the Chinese Society of Hematology, The OS and FFS rates of HID-HSCT were comparable with those of MRD- and MUD-HSCT. HID-HST showed a comparable OS and better FFS rate than IST.

Based on these available data, all children eligible for HSCT are recommended to undergo HLA typing at the time of diagnosis, followed by RD or UD searches to assess the availability of potential donors. Because acute and chronic GVHD have a lower incidence, MRD-HSCT is recommended as a first-line treatment when an MRD is available. If an MRD is unavailable, IST is recommended as a first-line therapy. If a suitable MUD can be identified rapidly, MUD-HSCT could become the upfront therapy. For emergent cases, UCBT or HID-HSCT can be considered as a front-line treatment.

# Conditioning Regimen for HCT in Severe Aplastic Anemia

Hawk Kim

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Hematopoietic cell transplantation (HCT) can achieve the robust recovery of depleted/destroyed blood cells in severe aplastic anemia (sAA). This advantage is usually reserved for relatively younger sAA patients having matched sibling donor. Recent successes of HCT from alternative donors such as matched unrelated donors and partially matched donors including haplo-identical family donors are translated to the performance of more and more HCTs from alternative donors even in older sAA. This trend also makes it difficult to decide how to optimize the conditioning regimen for HCT from these alternative donors and matched sibling donors as well.

The absence of malignant cells does not require graft-versus-malignant effect and also definitively tries to avoid graft-versus-host disease resulting application of reduced intensity conditioning regimens. High engraftment failure rate is limiting the minimal conditioning regimen dosage. These specific conditions require the pivotal role of the conditioning regimen in sAA as the secure restoration of active hematopoiesis while minimizing any possible complications of HCT.

The current standard conditioning regimen for younger sAA from matched sibling donor is cyclophosphamide (Cy) and anti-thymocyte globulin (ATG). However, further investigational trials suggest Cy-ATG is not the only option for these patients. Successful results of HCT from alternative donors, especially haplo-identical family donor increase its complexity. Arising questions are what's the best type of ATG, how to optimize the dosage of ATG/Cy and the possible stem cell manipulation such as  $\gamma/\delta$  cell depletion. We will discuss the issues in this lecture.



# Epstein Barr Virus in T-/NK-Cell Tumorigenesis

**Hiroshi Kimura**

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Epstein–Barr virus (EBV), which is associated with B-cell proliferative disorders/lymphomas, also transforms T- or natural killer (NK)-lineage cells and has related to various T-/NK- cell malignancies, such as extranodal NK/T-cell lymphoma-nasal type and aggressive NK-cell leukemia. Chronic active EBV disease (CAEBV), which occurs most often in children and young adults, is defined as an EBV-associated T/NK-cell lymphoproliferative disease in the 2017 WHO lymphoma classification. EBV-associated T-/NK- cell malignancies are refractory to conventional chemotherapies and have poor prognoses. Interestingly, these diseases are frequently seen in the East Asian countries. The role of EBV in tumorigenesis of T-/NK- cell lymphoid malignancies is still not clear. Recently, we performed comprehensive genetic analysis in patients with CAEBV to clarify its neoplastic nature and pathogenesis. The study revealed that somatic driver mutations (DDX3X and KMT2D) were found in EBV-infected cells, suggesting a unique role of these mutations in neoplastic proliferation of EBV-infected cells. Surprisingly, the EBV genome harbored frequent intragenic deletions that were common in various EBV-associated lymphomas, such as extranodal NK/T-cell lymphoma and EBV-positive diffuse large B-cell lymphoma. In this symposium, I summarize the lymphomagenesis and clinical features of EBV-associated T-/NK- lymphoid malignancies.

# Updates on EBV Positive Lymphoma

**Sylvain Choquet**

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Epstein Barr virus (EBV) is a pandemic virus, present in 95% of adults. Physiologically lurking in B lymphocytes, it is found in certain B lymphoproliferation of immunocompetent patients such as Hodgkin's lymphoma (HL) (30 to 50%) and Burkitt's lymphoma (BuL) (100% of endemic forms, 10 to 20% of sporadic forms), but it can also infect T cells and be at the origin of pathologies such as NK / T lymphomas and angioimmunoblastic T NHLs. In case of a predominant immunosuppression on T lymphocytes rather than B lymphocytes, the immunological balance is disrupted and EBV-infected B cells can proliferate and lead to lymphomas in the elderly, patients living with HIV and after organ or allogeneic stem cells transplantation (PTLD).

The involvement of EBV in immunocompromised patients is not constant, it is present in almost 100% of HL, but only 50% of BuL and 30% of diffuse large B cell lymphoma (DLBCL), it is found only in 50% of PTLDs, mainly in early forms. In contrast, EBV is present in almost 100% of cerebral lymphomas in both HIV patients and PTLDs.

The type of EBV antigens presented by the infected cell defines its type of latency, classified from 0 (only EBER positive) to III (multiple expressed antigens). Logically, the tumors of the immunocompetent patients are of low latency (BuL, HL), to avoid the immune response, unlike the tumors of the immunodepressed patients which are rather of latency II (HIV, NK / T) or III (PTLD).

The histological presentation is rarely different from the negative EBV forms, except for the immunocompetent HL where the forms with mixed cellularity are more frequent. On the molecular level, some features related to EBV have been described, as recently published, specific IgHV mutations in pediatric BuL.

Therapeutically, authors have proposed, in transplanted patients, antiviral preventive treatments, without proven efficacy, or anti CMV immunoglobulins (solutions also rich in anti EBV antibodies) with more success. In the transplanted patient, preemptive treatment, in the case of primary EBV infection or reactivation, has been proved effective by lowering immunosuppression and / or using rituximab. In curative treatment, the first lines are identical to those of EBV-negative lymphomas, but in the event of failure, anti-EBV T lymphocytes, most often allogeneic, are very promising.

# Treatment Strategies for Chronic Active Epstein Barr Virus Infection

Akihisa Sawada

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Chronic active Epstein-Barr virus (EBV) infection (CAEBV) is a representative disease of EBV-associated T- or NK-cell lymphoproliferative diseases (EBV+ T/NK-LPDs). Patients usually have recurrent fever and liver-enzyme elevation, sometimes accompanied with skin ulcers or large artery involvements (aneurysm and/or stenosis). Hypersensitivity to mosquito bites (HMB) and severe-type hydroa vacciniforme (sHV) are now regarded as CAEBV-related diseases. The patients with CAEBV are generally immunocompetent. High EBV load in the peripheral blood (PB) indicates CAEBV, and the definitive diagnosis is made with the evidence of EBV-infected T/NK cells in PB or in affected tissues.

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only cure. We reviewed 79 patients with CAEBV and its related diseases treated in our institute before March 2016. The 3-year overall survival rate (3y-OS) was  $75.8 \pm 4.8\%$  in total. Early symptoms can be controlled with steroids; however, with supportive care and steroids only, patients will die with disease progression including hemophagocytic lymphohistiocytosis (HLH) and organ failure, or will be in a high-risk or even in a difficult condition to undergo HSCT, in several years. Most of the patients, who had an active and advanced disease that was out of control with steroids and anti-cancer drugs, could not be rescued by emergent HSCT (3y-OS  $16.7 \pm 10.8\%$ ,  $n = 12$ ). For higher survival, we recommend to initiate treatment earlier to complete HSCT in advance.

The rate of rejection and mixed chimerism after allogeneic HSCT is higher in the patients with CAEBV than that in the patients with other diseases. However, myeloablative conditioning (MAC) is relatively toxic to the patients with CAEBV, and is inferior to reduced-intensity conditioning (RIC), as 3y-OS are  $66.7 \pm 14.7\%$  ( $n = 9$ ) and  $90.7 \pm 4.0\%$  ( $n = 54$ ), respectively ( $p < 0.05$ ). We established a 3-step strategy: step 1 (cooling) with steroids and cyclosporine A (CsA), step 2 (cytoreduction) with multi-drug chemotherapy, and step 3 with RIC followed by HSCT (RIC-HSCT). Etoposide is required for HLH. However, we have only 2 patients who achieved negative EBV load after chemotherapy and are enjoying continuous complete remission without HSCT. Step-2 may provide better disease control, and be a better bridge for preparation of HSCT. In addition, step-2 may contribute recipient-immune suppression for better engraftment.

Along the 3-step strategy, we have fine-tuned the RIC regimen: anti-thymocyte globulin (ATG) 2.5 mg/kg (1 week before HSCT), fludarabine 180 mg/m<sup>2</sup>, melphalan 140 mg/m<sup>2</sup>, and etoposide 200 mg/m<sup>2</sup>. For cord blood transplantation (CBT) after 3 or less courses of chemotherapy, melphalan 70 mg/m<sup>2</sup> was added (total 210 mg/m<sup>2</sup>); since then, no engraftment failure has been observed ( $n > 10$ ). Same 3-step strategy seems to work for adult patients; however, total body irradiation 3 Gy should be considered instead of additional melphalan 70 mg/m<sup>2</sup> that may cause severe stomatitis in adults.

# Posttransplant Lymphoproliferative Disorders: Did We Make More Progress?

**Ralf Trappe**

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Post-transplant lymphoproliferative disorders (PTLD) are a serious but rare consequence of immunosuppression after organ transplantation. Epstein-Barr virus (EBV) viral proteins or nucleic acids can often be demonstrated in tumor cells. The prevailing paradigm for the pathogenesis of PTLD is that the immunosuppression required to prevent graft rejection debilitates host T cell immunity and allows EBV-infected B cell blasts to proliferate unrestrained, thereby promoting tumorigenesis. The incidence of PTLD is significantly increased in patients after organ transplantation compared to non-Hodgkin lymphoma in the immunocompetent host. The rarity of PTLD, as well as the variety of histological manifestations and the complex medical history of PTLD patients have slowed the development of evidence-based therapies. While the histological range stretches from polymorphic PTLD to monomorphic lymphoma-type PTLD, the majority of cases are of CD20-positive B-cell lineage.

Immunosuppression reduction after diagnosis of PTLD has the goal of reestablishing host T-cell function sufficiently to control lymphoproliferation without compromising the grafted organ and has been reported to yield high response rates (45%) in a retrospective analysis. On the other hand, the only prospective trial conducted so far demonstrated a response to immunosuppression reduction in one out of sixteen cases (6%). Current recommendations for immunosuppression reduction are based on guidelines originally formulated for renal transplant recipients: Stop antimetabolites (azathioprine and mycophenolate), reduce calcineurin inhibitors by 25-50% and maintain corticosteroids. However, data from prospective clinical trials have shown that corticosteroid-containing immunosuppression after diagnosis of PTLD is associated with an increased risk of relapse whereas the use of antimetabolites is not.

Case reports and small case series remain the only source of evidence for the clinical management of rare subtypes and the relapsed/refractory setting. However, for the most common subtype, CD20-positive B-Cell PTLD, which accounts for 80% of cases, a succession of prospective clinical phase II trials has led to a successful, evidence-based standardized treatment protocol in patients after solid organ transplantation (SOT). Initial, small trials of rituximab monotherapy had resulted in an overall survival of 1.2 to 3.5 years in patients with PTLD after SOT. In 2007, the PTLD-1 trial demonstrated the safety and efficacy of sequential treatment with 4 cycles of weekly rituximab followed by 4 cycles of CHOP-21 chemotherapy in 70 patients with CD20-positive PTLD after SOT. Median overall survival was 6.6 years and response to four cycles of rituximab induction was a prognostic factor for OS after completion of sequential therapy. Finally, a trial of risk-stratified sequential treatment with rituximab consolidation for patients in CR after rituximab induction

(low-risk group) and R-CHOP-21 (rituximab and CHOP-21; high-risk group) for patients not in CR after four weekly cycles of rituximab demonstrated in 2016 that complete response to rituximab induction identifies a group of patients with B-cell PTLD who do not need chemotherapy.

Based on retrospective case series rituximab monotherapy combined with immunosuppression reduction also is effective after HSCT with positive outcomes in about 70% of patients. However, chemotherapy after HSCT is not recommended as first-line therapy due to poor tolerability and the risk of inducing neutropenia and graft failure.

SOT patients failing to respond to sequential treatment and HSCT patients failing to respond to rituximab monotherapy have a very poor prognosis. With conventional chemotherapy median overall survival is less than 3 months and two-thirds of patients ultimately die. Half of the deaths are from PTLD and 25% from treatment-related causes.

The use of donor derived virus-specific cytotoxic T-cells can effectively restore EBV-specific immunity and control viral infection. Early proof of principle studies demonstrated that the administration of donor-derived T cells specific for cytomegalovirus or Epstein-Barr virus could effectively restore virus-specific immunity and control viral infections. Subsequent studies using different expansion or direct selection techniques have shown that donor-derived virus specific T-cells confer protection in vivo after adoptive transfer. More recent studies have infused closely matched third-party EBV-specific T-cells and reported high response rates and a 1-year overall survival of 60 to 70%. Responding patients showed long lasting responses with a median overall survival not reached at a median follow up of 3 years. Patients included had PTLD refractory to rituximab (HSCT cohort) or refractory to rituximab and CHOP (SOT cohort).

# Prognostic Significance of NGS-Based Minimal Residual Disease in the Setting of SCT in Leukemia

**Borahm Kim**

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Acute leukemia is one of common types of hematologic malignancy. Molecular genetic tests such as gene fusion study have critical role in diagnosis and treatment decision in patients with acute leukemia along with cytopathologic examination. Since morphologic examination often results in insufficient sensitivity and not all patient are harboring gene fusions, however, more sensitive and universal marker is needed. In case of patients with acute lymphoblastic leukemia, rearrangement of immunoglobulin heavy chain and light chain are considered as universal marker representing monoclonality of B-cell population and thus the presence of residual disease, and the use of immunoglobulin clonality tests is expanding with advance of next-generation sequencing (NGS) technology. Technically, with use of NGS, the sensitivity could reach as high as detection of one in  $10^5$  to  $10^6$  cells and a number of clinical reports confirmed that the clinical outcome correlates with the results of the test. It could affect the clinical decision on choice of treatment and stem cell transplantation. In this talk, NGS method for disease monitoring focusing on immunoglobulin clonality assay will be introduced.

# A Practical Application and Limitation of NGS Based HLA Typing for SCT

Yun Ji Hong

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Recent advanced in next-generation sequencing (NGS) has led to development of whole-genome analysis in individuals. Researches on human leukocyte antigen (HLA) and the relation with transplantation outcomes have received benefit from the technologies. In this lecture, the principle, the benefit, the clinical application and the limitation will be discussed.

## 1. Long-range PCR in NGS based HLA typing

The PCR has been one of the most essential techniques in HLA typing to clone small DNA fragments. Traditionally, amplicon size of PCR reaction was limited to 200–1000 bp. By modifying the polymerase, the size of amplicons increased up to over 30 kb. The majority of commercial HLA typing assay for NGS uses long-range PCR as the amplification method. While traditional Sanger sequencing for HLA typing usually targets exon 2-4 of *A*, *B*, *C* locus, exon 2 of *DRB1* locus, exon 2-3 of *DQB1* locus, long-range PCR covers almost full length of each locus. Covering wide region of HLA gene, long-range PCR decreases ambiguities of HLA type.

## 2. Determination of the phase and location

While sequence-based HLA genotyping has become routine, only 7% of the HLA genes have been characterized by allele-level sequencing, while 93% are still defined by partial sequences. Sanger sequencing is unable to determine the cis-trans phase of the exon. In contrast, parallel sequencing of NGS clearly discriminate the phase of exon. By discrimination alleles, the ambiguities in HLA allele combination has been resolved.

## 3. High throughput of NGS system

HLA genomic region is located on chromosome 6p21 and encodes more than 200 genes. There are also non-classical HLA genes, such as *HLA-DO*, *DM*, *E*, *F*, *G*, *MICA* and *MICB* as well as classical *HLA-A*, *B*, *C*, *DPA1*, *DPB1*, *DQA1*, *DQB1*, *DRA*, and *DRB1*. Massive parallel sequencing methods, allowing larger-scale production of genomic sequence, which allows simultaneous detection of a various range of *HLA* genes.

## **4. Application of NGS based HLA typing in stem cell transplantation**

In the process of unrelated allogeneic stem cell transplantation, there is mandatory confirmatory test for donor HLA type using donor's newly acquired blood sample. Cases of discrepancies between the result at the recruitment and that of confirmatory testing occasionally occurs. According to Baier et al, lower overall erroneous rate of donor HLA result would be expected by adopting NGS-based HLA typing at recruitment. NGS-based HLA typing and matching up to ultra-high resolution level in donor-recipient pairs in stem cell transplantation showed better outcome. Ultra-high resolution levels includes exons outside of antigen recognition domain, introns, and untranslated regions.

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*For the best stem cell transplantation*

# Special Symposium



# Haploidentical Stem Cell Transplantation: Where are We Now?

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Haploidentical stem cell transplantation (Haplo-SCT) is currently a suitable alternative worldwide for patients with hematological diseases, who lack HLA-matched siblings or unrelated donors.

Recently, Haplo-SCT is now widely accepted going to its excellent outcomes and its inherited advantages in comparison to MUDT and UCBT. In China, as compared with MSDT, Haplo-SCT has become the largest donor source, and now is used in almost 48% of allo-SCTs. In Europe, the use of haploidentical family donors has continuously increased to 25%. In the USA, HID is the only donor type showing an increase, compared with all the other donor types showing a decline or stability in use in 2015.

Currently, there are currently 3 major approaches for Haplo-SCT: Beijing protocol G-CSF-based experience; Baltimore protocol PT/Cy, and *in vitro* TCD with mega-dose CD34+ cell transplant. All the aforementioned three haploidentical transplant modalities have advantages and disadvantages. Beijing protocol is also associated with very low relapse rates and low incidence of graft failure, and has benefited more than half the world's Haplo-SCT recipients. The PT/Cy-based approach can be applied to either reduced intensity or myeloablative regimens, and has a very low incidence of both acute and chronic GVHD. The advantages of the TCD protocol include low GVHD and high quality of life; however, its disadvantages include high incidence of graft failure, slow IR then high incidence of infection and a fairly high relapse rate in acute lymphoblastic leukemia.

Currently, the Beijing Protocol and the Baltimore Protocol are the mainstream strategies in Haplo-SCT. However, evidence regarding the superiority of one protocol to another is lacking.

The goal for Haplo-SCT is to cure underlying disease without TRM. This goal comprised improving immune reconstitution to reduce NRM, reducing GVHD without impair GVL impact, and reducing relapse rates. All the improvement aimed to reduce NRM and relapse will finally translated into improved OS and quality of life.

# Progress of CAR-T Cell Therapy for Hematologic Malignancy

**Xiaojun Huang**

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Chimeric antigen receptors (CARs) are receptor proteins that have been engineered to give T cells the new ability to target a specific protein. US Food and Drug Administration (FDA) approved CD19-targeted CAR-T cells to treat B-cell acute lymphoblastic leukemia and lymphoma in 2017. Numbers of clinical study demonstrated that it showed profound therapeutic effect. As a cutting-edge technology for leukemia therapy, it not only provides new methods for hematologic malignancies treatment, but also provides opportunities for clinical research.

The research and development of CAR-T therapy not only includes in vector construction, but also the innovation of targets and structures. Second generation of CAR-T is the most widely used for B-cell acute lymphoblastic leukemia and lymphoma. As for targets, CD19 is the most used target, followed by CD22, while other targets are BCMA, CD20, CD30, CD33, etc., which need to further verify its safety and effectiveness. For cell source, most studies focus on autologous CAR-T, while more and more studies have interest in allogeneic CAR-T cell therapy. As for CAR-T structure, Scholars from China reduced the immunogenicity of CARs by using humanized scFv, which improved the longevity of CAR-T cell persistence and enhanced their therapeutic efficacy in patients. By May 2019, there are 142 CAR-T clinical trials registered in China, while 122 CAR-T clinical trials registered in US, making China with the most CAR-T clinical studies in the world. Long-term follow-up study of CD19 CAR-T therapy in acute lymphoblastic leukemia showed that its remission rate is high, but some studies reported that its high relapse after CAR-T infusion is also a problem.

Hematopoietic stem cell transplantation (HSCT) has multiple mechanisms against leukemia. As the same time, multiple cell types involve in different phases in the process of HSCT. On the one hand, as an effective treatment, CAR-T immunotherapy can be applied in the early stage of treatment for leukemia to achieve complete remission, then bridged to transplantation to achieve the best effect. On the other hand, CAR-T is effective and safe for patients with relapsed B-ALL after HSCT. However, long-term follow-up of CD19 CAR-T in B-ALL after HSCT by Peking University suggested that relapse rate after CAR-T infusion is high. Therefore, how to choose next treatment strategy for these patients is also a problem we should consider. In conclusion, CAR-T immunotherapy is another platform following chemotherapy and HSCT, which is beneficial to comprehensive therapy for hematologic malignancies. Significant short-term effect has been shown in CAR-T cell therapy. However, it may be difficult to substitute HSCT in a long term.

# Role of Hematologist in Radiation/Nuclear Emergency: An Experience of the Tokai-mura Accident

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## Introduction

Whole-body exposure to high-dose radiation results in injury involving multiple organs that depends on their sensitivity to radiation. This is the so-called acute radiation syndrome (ARS), which is caused by the brief exposure of a major part of the body to radiation at a relatively high dose rate. During this decade, on the other hand, few accidents causing severe ARS have been experienced. However, there has been no consensus on any treatment strategy of ARS and little literature on radiation accidents describing the nature of the pathophysiology, which may be necessary for treatment of heavily irradiated patients. This lecture will review a Japanese accident which had occurred in 1999 and discuss the treatment strategy for bone marrow injury in ARS.

## An accident

On 30 September 1999, a criticality accident occurred at the uranium conversion facility in Tokai-mura located 130 km northeast from Tokyo, Ibaraki Prefecture, Japan (1). The criticality event occurred when 3 workers were pouring a solution of enriched  $^{235}\text{U}$  into a precipitation tank directly. They bypassed a dissolution tank and buffer column supposed to be used in order to avoid criticality; an amount of uranium was several times more than the specified mass limit. At the accident, these workers were severely exposed  $\gamma$ - and neutron-irradiation. The estimated doses were 24.5 GyEq (Gy equivalent to  $\gamma$ -ray), 8.3 GyEq, and 3.0 GyEq. Despite of all medical efforts including stem cell transplantation, 2 workers died 83 and 211 days after the accident. This accident showed that ARS could lead to multiple organ failure (MOF).

## Concept of ARS and hematopoietic stem cell transplantation (HSCT)

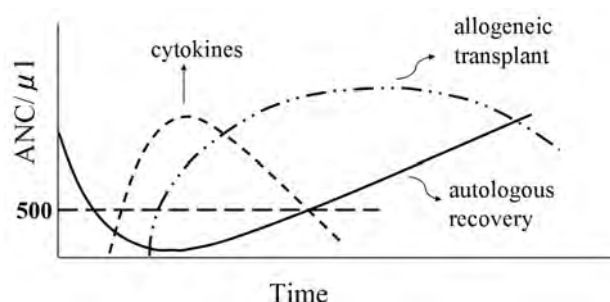
A new strategic approach to the diagnosis of ARS was proposed by a group of experts from European countries, based on knowledge and experience from previous radiation accidents (2). The approach proposes that the 4 organ systems should be considered of critical significance for the development of ARS; hematopoietic, skin, gastrointestinal, and neurovascular systems are the most important organs. On the other hand, there are several problems to be considered in terms of the treatment of bone marrow injury. Unlike

therapeutic whole-body irradiation, radiation in the accidental exposure is always heterogeneously delivered, indicating the presence of functional residual hematopoiesis. Autologous hematopoietic recovery is possible. This is a key point for making decisions as to whether HSCT or cytokine therapy should be performed. Experiences of prior radiation accidents suggest that the role of HSCT, especially bone marrow transplantation, is limited and the outcome of HSCT is poor despite transient engraftment with partial chimerism. In the Tokai-mura accident, one victim exposed to approximately 10 GyEq of neutrons and  $\gamma$ -rays received an HLA-DRB1, mismatched, unrelated umbilical cord blood transplant (3). While donor/recipient mixed chimerism was attained and this victim experienced rapid autologous hematopoietic recovery, he had persistent and profound immune deficiency (4). There were increases in naive T cells and helper T-cell subtype 1, but the mitogenic responses of T cells and the allogeneic mixed leukocyte reaction were severely suppressed. Endogenous immunoglobulin production remained low until 120 days after the accident and he died of MOF 211 days after the exposure. Thus, there is a problem to be resolved in recovered bone marrow, and the mechanisms are not clear. On the other hand, limited success of an allogeneic HSCT may lead to damage to other organ systems such as the lungs and the gastrointestinal tract. An early transplant can lead to severe graft versus host disease (GVHD) that victims cannot tolerate. Thus, a treatment strategy for bone marrow is an issue calling for extensive and far-reaching discussion.

### **Future direction for treatment of hematopoietic system**

The European Group for Blood and Marrow Transplantation (EBMT), in cooperation with the Institute for Radiation Protection and Nuclear Safety (IRSN, France) and the University of Ulm (Germany) has proposed a treatment strategy for bone marrow injury by radiation (5). They held a consensus conference on the medical management of mass radiation accidents in October 2005, at Vaux de Cernay Abbey in France. At the meeting, a consensus was reached on the issue of HSCT; HSCT should not be performed on any radiation accident victim with the potential of endogenous hemopoietic recovery. Since most accidents deliver heterogeneous irradiation and autologous hematopoietic recovery is always a possibility, whether or not to perform HSCT is not an emergency decision, and it requires careful consideration of the possible risks involved. Furthermore, patients with multi-organ dysfunction syndrome (MODS) might not tolerate early transplant due to their co-morbidities. It was also suggested that the transplantation itself should not be carried out before a minimum observation period of 14 to 21 days had elapsed.

On the other hand, a limited dose range for which HSCT should be considered as a therapeutic option for victims in a large-volume scenario has been also proposed (6). They recommended that for relatively low doses (2-4 GyEq), endogenous recovery of autologous hematopoiesis can be expected, but victims receiving higher doses (6-10 GyEq) may require allogeneic hematopoietic cell support from peripheral blood or cord blood. This group also suggested that the use of donor cells is sufficient for survival from acute hematopoietic syndrome associated with these higher doses of radiation. Therefore, the immediate needs of such patients (recovery of myelopoiesis) can be supported by the transient engraftment of donor cells. Thus, it would be possible to perform HSCT as "a bridge to autologous recovery" (Figure).



**Figure.** A bridge to autologous recovery of bone marrow after radiation exposure. ANC, absolute neutrophil count. Adapted and modified from Ref. 6.

## Treatment of heavily exposed persons

The radiation level causing irreversible failure of bone marrow is not clear. There are reports on the auto-recovery of bone marrow in patients exceeding 10 GyEq but not 12 GyEq. In victims of very high doses, probably over 12 GyEq, serious radiation injuries to regions other than bone marrow, such as lungs, gastrointestinal tract and skin, increase the risk of fatal MOF, even if bone marrow has been successfully controlled (1). Treatment of these organs is not established, and the prognosis of these victims is very poor. Time when each country or region should discuss a treatment strategy for bone marrow injury by radiation has come.

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# Sustainable Medical Preparedness and Response System for Radiation Emergencies in Republic of Korea

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This session provides information about the medical preparedness and response system for radiation emergencies in Republic of Korea. The National Radiation Emergency Medical Center (NREMC) oversees medical affairs in the Korean radiological disaster prevention system since its establishment in 2002. It has dedicated itself to set up a nationwide radiation emergency medicine network with 24 designated radiation emergency hospitals. NREMC, as one division under the Korea Institute of Radiological And Medical Sciences (KIRAMS), provides efficient medical care to patients suspected with radiation exposure by collaborating with professional medical staffs in Korea Cancer Center Hospital (KCCH). For prompt response to radiation accidents, NREMC has offered specialized trainings for medical staffs and first-responders. It has also operated the 24 hour on-call system to consult public concerns of radiation exposure, which can be switched into an emergency mode upon receiving accident reports. In addition, NREMC has conducted dose assessments of radiation exposure with high level of accuracy, and implemented R&D programs for radiation injury therapeutics and low-dose radiation risks evaluation in daily life. NREMC supports global initiatives for strengthening medical preparedness and response for radiation emergencies with international organizations.

# Cytopenia: Clonal vs Immune-A Guide to Investigation and Management

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# Gene Corrected Autologous Hematopoietic Stem Cells for Therapy of Blood Diseases - Challenges to Its Application in the Asia Pacific Region

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Gene corrected autologous hematopoietic stem cell transplantation (HSCT) has been used to successfully treat patients with immune deficiency disorders for nearly three decades. More recently, lentiviral vector based gene replacement therapy has been successfully achieved for the major hemoglobin disorders (MHD) also. In fact, two lentiviral vector based gene therapy products have been licensed in Europe during the last year for the above conditions. However, they cost between € 0.75 to 1.5 million per dose. Several more clinical trials are underway with similar products to develop further options for gene therapy for the MHD. Early data from these trials have confirmed the previous observation that 4-10 G/dl enhancement of the baseline hemoglobin occurs within a few weeks of gene therapy in most of these patients. An alternative approach is gene editing of specific targets within the globin gene cluster. A successful target for this approach has been the disruption of the BCL11A transcription factor which down regulates the  $\gamma$  globin gene after birth to shut down HbF production. Clinically significant elevations of HbF have been achieved with this approach in pre-clinical studies - enough to justify initiation of clinical trials. In the Asia Pacific (APAC), MHD present a major public health problem for which the only curative therapy so far has been allogeneic HSCT. Even though available for more than three decades, access to alloHSCT has been limited in the APAC region related to many reasons including lack of suitable donors, complexity of the treatment, associated complications, lack of trained personnel as well as adequate infrastructure and cost. The option of autologous gene corrected HSCs could be a game changer for these patients. However, for that to happen, there is a need to develop these technologies in a manner that the costs of such products, when approved, are affordable by patients in the APAC. We are developing both lentiviral vector based gene replacement therapy as well as CRISPR-Cas9 based gene editing approach to alleviate low hemoglobin levels in MHDs. We have also developed another novel lentiviral vector based gene replacement therapy for the treatment of hemophilia A. A suitable FVIII transgene with CD68 related promoter has been developed and tested in pre-clinical models. The data was found sufficient for initiating a Phase 1 clinical trial. Developing appropriate technology for gene therapy locally, along with the capacity to produce high quality vectors within appropriate GMP facilities, is critical for providing access to these novel therapies to patients in the APAC region.

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# Education Session



# Autologus HSCT in Waldenström's Macroglobulinemia

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The role and timing of autologous stem cell transplantation (ASCT) in Waldenström's Macroglobulinemia (WM) has not been well established. WM is a highly chemo-sensitive disease and many of responses are durable. However, almost all patients will eventually progress and incurable. Given the excellent outcomes with novel agents introduced in the recent years, ASCT is not appropriate treatment option as front line treatment, but ASCT should be considered in second line treatment since ASCT can be expected to achieve deep and long-lasting remission and is less expensive compared to novel agents. ASCT may not effective as a late salvage treatment and stem cell collection will be challenging in heavily treated patients with stem cell toxic agents such as alkylating agents and purine nucleoside analogs. In the European Bone Marrow Transplant Registry data, the largest registry data on ASCT in WM, including 158 WM patients transplanted between 1991 and 2005, 5-year progression free survival (PFS) and overall survival(OS) were 39.7% and 68.5%, respectively. For patients transplanted at first response, PFS at 5years was 44%. Toxicity was acceptable with non-relapse mortality at 1 year of 3.8%. Having received at least three prior lines of therapy before ASCT and having refractory disease at ASCT were associated with a significantly inferior PFS and OS. Mayo Stratification of Macroglobulinemia And Risk-adapted Therapy (mSMART) guideline recommends that stem cell collection for future use in first plateau may be appropriate for patients 70 years or younger and ASCT should be considered for first or second relapse in transplant-eligible patients with chemo-sensitive disease. The consensus on indication for ASCT in WM produced by international experts from the EBMT lymphoma working party, European Consortium for WM (ECWM) and International WM foundation (IWMF) was presented at the 2018 EBMT Annual Meeting. The key consensus outcomes are followings: i) ASCT could be considered as a treatment option for patients with more than two relapses and chemo-sensitive disease, ii) ASCT is not appropriate as part of first-line therapy for WM patients who are responding to their induction therapy and also to B-cell receptor inhibitors, iii) Stem cell toxic agents should be avoided in first-line therapy in patients with the potential for ASCT. ASCT is an effective but underutilized option for salvage therapy in WM and decision for ASCT should be based on the clinical course of the disease.

# Maintenance Therapy Post 1st Autologous Transplantation

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Post ASCT treatment has demonstrated importance to significantly improve survivals in the context of our understanding of the tumor mass remaining in the bone marrow of the patients and the interactive role of the bone marrow microenvironment with the tumor cells e.g. need to restore the immune control of the clonal compartment and maintain disruption of the crosstalk between the tumor cells and their microenvironment. The exact significance and role of consolidation versus maintenance can be discussed at length, but the importance of at least the use of maintenance is now considered a standard of care.

The current paradigm, based on the clinical trials performed, has showed that maintenance with the oral compound Lenalidomide low dose daily until progression was safe enough at short and long term and significantly prolonged survival. Ongoing studies challenge the need for a continuous Imids with the oral proteasome inhibitors Ixazomib, given that studies with the first in class PI Bortezomib had in the past demonstrated benefits particularly in some high-risk subgroups, however, neurological toxicity had put a break on this development. The most recent anti CD38 naive immunotherapy has put some light on a possible immunoreset mechanisms of action and consequently brought some interest into studying Daratumumab as a maintenance option as well.

Still, despite years of demonstrating this benefit of post transplant treatment action, so many questions remain unanswered. The type of drug and mechanisms of action might be of importance for certain subtypes of Myeloma, similarly, the need for combinations of drugs and therefore mechanisms of action. The exact duration is also source of question, until progression for all, or limited to some, but then what are the underlying mechanisms to explain the possibility to shorten duration of maintenance and still gain similar survival impact. Recent studies have started looking into providing answers to some questions, including the possibility to identify markers of excellent and deep responders with prolonged tumor control, possibly immunorestitution against the tumor clone, e.g. using MRD as a marker for shortening the duration of the post transplant period of treatment. Some would argue that patients in significant prolonged MM control and deep sustained negative MRD would be the patients to anticipate early stop of treatment, while other would propose that these patients that have particularly benefited from the treatments should remain on treatment as possibly operationally cured.

Finally, the concept is going to have to be entirely rewritten with the advent of the active/armed immunotherapy, CAR T, BITE and ADCs.

## New Insights in GVHD Prophylaxis

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Graft versus host disease (GVHD) remains the principal limiting factor of allogeneic hematopoietic stem cell transplantation (HSCT). The pathophysiology of GVHD is complex, however the main therapeutic approaches developed so far for the prevention of GVHD are focused on the partial inhibition of T cell activation. The basic prevention of GVHD includes the association of drugs inhibiting the two main pathways of T cell activation: calcineurin inhibitors (such as ciclosporin A and tacrolimus) and T cell proliferation inhibitors (such as methotrexate, mycophenolate mofetil or sirolimus). More recently, the addition of anti-thymoglobulin (ATG) has been shown in prospective randomized studies to be able to reduce the incidence of acute and chronic GVHD. However, the use of ATG increases the risk of viral infections; and may increase the risk of relapse in some transplantation contexts such as sibling donors or reduced intensity conditioning (RIC). One way to better find the good balance with ATG between prevention of GVHD and infection/relapse risks could be to adapt the dose of ATG to lymphocyte counts, based on PK analyses. Even more recently, the use of high dose cyclophosphamide on days 3 and 4 after transplantation (PT-Cy) in association with CsA and MMF, has fundamentally changed the scope of haplo-identical HSCT. This approach seems to be interesting in transplants performed with HLA 9/10 mismatched unrelated donors. Several studies using PT-Cy have been performed with HLA matched related or unrelated donors. Incidences of acute GVHD remain above 50% in all studies with PT-Cy alone, but the association of PT-Cy + Tacrolimus and MMF is associated with low risks of GVHD and promising overall survival in single center or retrospective studies. The question whether PT-Cy could replace ATG in HLA matched allo-HSCT should be answered by prospective randomized studies analyzing immune reconstitution and long term outcomes. Finally, I will introduce other ways of research are ongoing in the field of GVHD prevention: JAK inhibitors, administration of immunosuppressive cells or restoration of gut microbiota dysbiosis. In conclusion, progresses need to be performed in the prevention of GVHD without impairing the graft-versus-leukemia effect. Studies analyzing PK of ATG, identifying the best combination with PT-Cy or modulating gut microbiota are of particular interest.



# New Agents in GVHD Treatment

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## Learning Objectives

1. Novel strategies to inhibit signaling pathways that promote GVHD have been developed from the mouse model into early clinical trials.
2. Tissue regenerative approaches that promote healing of GVHD related tissue damage in thymus, intestinal tract and skin and microbiota-modification hold promise to extend the immunosuppression-based acute GVHD therapy approaches.

## Abstract

Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative treatment for different hematological malignancies. A major life-threatening complication is acute graft-versus-host disease (GVHD) in particular when the disease becomes steroid refractory (SR). Based on the detection of pathogenic cytokines, chemokines and T cell subsets in individuals developing GVHD or experimental GVHD models, different therapeutic strategies have been developed. A potential cause why targeting individual receptors can lack efficacy could be that multiple cytokines, danger signals and chemokines are released during GVHD which have redundant functions. To overcome this redundancy, novel strategies that do not target individual surface molecules like chemokine receptors, integrins and cytokine receptors, but instead inhibit signaling pathways downstream of these molecules have been tested in preclinical GVHD models and are currently tested in clinical GVHD trials. Another important development are tissue regenerative approaches that promote healing of GVHD-related tissue damage as well as strategies that rely on microbiota modifications. These approaches are promising as they act very different from conventional immunosuppression and rather aim at reinstalling tissue homeostasis and microbiome diversity.

This review discusses major novel developments in GVHD therapy which are based on a better understanding of GVHD biology, the repurposing of novel kinase inhibitors, microbiome modification strategies as well as tissue regenerative approaches.

# Revised WHO Classification and Genomics: Acute Leukemia and Myelodysplastic Syndrome

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The World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues was revised in 2016, due to the advances in the identification of unique biomarkers associated with some myeloid neoplasms and acute leukemias, derived from gene expression and next generation sequencing data. In this session, I will talk about the revised WHO classification on acute leukemias and myelodysplastic syndrome. Table below shows the WHO classification of myelodysplastic syndromes and acute leukemia revised in 2016.

## Part 1: Myelodysplastic syndrome

Myelodysplastic syndromes are a group of clonal hematopoietic disorders characterized by ineffective hematopoiesis, morphologic dysplasia and peripheral cytopenia. Cytopenia is required for any MDS diagnosis. The threshold to define dysplasia remain as 10% dysplastic cells in any hematopoietic lineage. Changes made in the revised classification for MDS are as below.

- 1) Nomenclature: Previous nomenclature included references to "cytopenia", but specific cytopenias have minor impact. Thus, the terminology for adult MDS has changed to "MDS" followed by single vs. multilineage dysplasia, ring sideroblasts, excess blasts, or del(5q).
- 2) Diagnostic criteria for MDS with ring sideroblasts (RS): MDS-RS includes single and multilineage dysplasia. If *SF3B1* mutation is identified, one can diagnosis MDS-RS even if RS is only present  $\geq 5\%$ .
- 3) MDS with isolated del(5q): 1 additional chromosomal abnormality can be present in addition to del(5q). However, the additional abnormality cannot be monosomy7 or del(7q).
- 4) Blast percentage: The denominator used for calculating blast percentage in all myeloid neoplasms is all nucleated BM cells, not just the "nonerythroid cells."

## Part 2: Acute leukemia

The WHO continues to define specific acute leukemia disease entities by focusing on significant cytogenetic and molecular subgroups.

AML with recurrent genetic abnormalities: A large number of recurring, balanced cytogenetic abnormalities are recognized in AML. Gene mutations with prognostic significance have been considered for the incorporation into the classification and *NPM1*, bilallelic *CEBPA*, (provisional) *RUNX1* mutation are included.

AML with myelodysplasia related changes is an acute leukemia with  $\geq 20\%$  of blasts, with morphological features of myelodysplasia, or occurring in patients with a prior history of a MDS or MDS/MPN, or with MDS

WHO myeloid neoplasms and acute leukemia classification
<b>Myelodysplastic syndrome (MDS)</b>
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
<i>Provisional entity: Refractory cytopenia of childhood</i>
<b>Myeloid neoplasms with germline predisposition</b>
<b>Acute myeloid leukemia (AML) and related neoplasms</b>
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1); <i>RUNX1-RUNX1T1</i>
AML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); <i>CBFB-MYH11</i>
APL with <i>PML-RARα</i>
AML with t(9;11)(p21.3;q23.3); <i>MLLT3-KMT2A</i>
AML with t(6;9)(p23;q34.1); <i>DEK-NUP214</i>
AML with inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2); <i>GATA2, MECOM</i>
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); <i>RBM15-MKL1</i>
<i>Provisional entity: AML with BCR-ABL1</i>
AML with mutated <i>NPM1</i>
AML with biallelic mutations of <i>CEBPA</i>
<i>Provisional entity: AML with mutated RUNX1</i>
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome
<b>Blastic plasmacytoid dendritic cell neoplasm</b>
<b>Acute leukemias of ambiguous lineage</b>
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); <i>BCR-ABL1</i>
MPAL with t(v;11q23.3); <i>KMT2A</i> rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
<b>B-lymphoblastic leukemia/lymphoma</b>
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); <i>BCR-ABL1</i>
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); <i>KMT2A</i> rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); <i>ETV6-RUNX1</i>
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.1); <i>IL3-JGH</i>
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); <i>TCF3-PBX1</i>
<i>Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like</i>
<i>Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21</i>
<b>T-lymphoblastic leukemia/lymphoma</b>
<i>Provisional entity: Early T-cell precursor lymphoblastic leukemia</i>
<i>Provisional entity: Natural killer cell lymphoblastic leukemia/lymphoma</i>

related cytogenetic abnormalities; recurrent genetic abnormalities as described in "AML with recurrent genetic abnormalities" should be absent and also prior cytotoxic or radiation therapy for an unrelated disease should be absent.

Therapy-related myeloid neoplasm includes t-AML, t-MDS, t-MDS/MPN that occur as a late complication of cytotoxic therapy and/or radiation therapy administered for a prior neoplastic or non-neoplastic disorder. Cytotoxic agents implicated in therapy-related myeloid neoplasm include alkylating agents, ionizing radiation therapy, topoisomerase II inhibitors and some antimetabolites and anti-tubulin agents.

Myeloid sarcoma: A tumor mass consisting of myeloid blasts, with or without maturation, occurring at an anatomical site other than the bone marrow.

Myeloid neoplasms with germline predisposition: A new section added in the revised WHO classification. Myeloid neoplasms with germline predisposition are classified into those without a pre-existing disorder or organ dysfunction (germline *CEBPA*, *DDX41* mutation), or with a pre-existing platelet disorders (germline *RUNX1*, *ANKRD26*, *ETV6* mutation), or with other organ dysfunctions (germline *GATA2*, bone marrow failure syndrome, telomere biology disorders, Down syndrome).

B-cell lymphoblastic leukemia/lymphoma is a neoplasm of precursor lymphoid cells committed to the B cell lineage, involving bone marrow and blood (B-ALL) and occasionally presenting with primary involvement of nodal or extra-nodal sites (B-LBL). Provisional entity of B-ALL with intrachromosomal amplification of chromosome 21 have been added, which is present in 2% of children ALL and is associated with an adverse prognosis. It is a neoplasm of lymphoblasts characterized by amplification of a portion of chromosome 21, typically detected by FISH with a probe for *RUNX1* that reveals  $\geq 5$  copies of the gene (or  $\geq 3$  extra-copies on a single abnormal chromosome 21). *BCR-ABL1* like ALL is newly added with its association with and adverse prognosis and responses of some cases to tyrosine kinase therapies.

T-cell lymphoblastic leukemia/lymphoma is a neoplasm of lymphoblasts committed to the T-cell lineage. One of the provisional entities newly added includes, early T-precursor ALL, which shows early T cell differentiation with retention of myeloid and stem cell characteristics both immunophenotypically and genetically. By definition, blasts in ETP-ALL express CD7 but lack CD1a and CD8, and are positive for 1 or more of the myeloid/stem cell markers CD34, CD117, HLADR, CD13, CD33, CD11b, or CD65.

# Revised WHO Classification and Genomics: Non-Hodgkin Lymphoma

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World health organization (WHO) revised lymphoma classification in 2016. In this new edition, several new terminologies and concepts have been suggested and diagnostic criteria are refined for some entities. Furthermore, a limited number of new provisional entities are added. Here, we will overview of previous and current classifications of lymphoid tumors, touching on new and controversial entities.

# GD2-Targeted Immunotherapy of Neuroblastoma

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Although the development of cancer immunotherapeutics is flourishing, the list of targets of approved agents has been short and limited to protein molecules. The approval of Dinutuximab, a chimeric anti-GD2 antibody, ch14.18, in combination with GM-CSF and IL2 for the treatment of high-risk neuroblastoma after stem cell transplant in 2015 marks the first new agent targeting a glycolipid molecule, thereby widening the net of potential pharmaceutical targets. This was largely based on the pioneer work of Dr. Yu and her leadership during the entire course of ch14.18 development sponsored by National Cancer Institute and Children's Oncology Group (COG). She led the pivotal phase III randomized clinical trial of ch14.18 + IL-2/GM-CSF in high risk neuroblastoma patients after completing stem cell transplant and radiotherapy. Among 226 randomized patients, the 2-year event-free survival ( $66 \pm 5\%$  versus  $46 \pm 5\%$ ,  $p = 0.01$ ) and overall survival ( $86 \pm 4\%$  versus  $75 \pm 5\%$ ,  $p = 0.02$ ) were significantly higher for patients randomized to immunotherapy + isotretinoin than those treated with isotretinoin alone. Subsequently, ch14.18 produced in CHO cells (Dinutuximab-beta) showed similar efficacy for high risk neuroblastoma in a randomized SIOPEN study whether IL2 was added or not (Lancet 2018). This led to the approval of Dinutuximab-beta in 2017 in EU. Recently, COG conducted a phase II selection design trial in patients with relapsed/refractory neuroblastoma. Eligible patients were randomly assign patients to irinotecan and temozolomide plus either temsirolimus or dinutuximab + GM-CSF. Irinotecan-temozolomide- dinutuximab + GMCSF (I/T/DIN/GM-CSF) shows superior anti-tumour activity with 9/17 (53%) patients showing objective responses, vs. 1/18 (6%) patients treated with I/T/DIN/GM-CSF (Lancet Oncology, 2017). The trial was expanded to recruit additional 36 patients non-randomly assigned to I/T/DIN/GM-CSF. In total, 22/53 patients showed objective responses (41.5%) (ASCO 2018). The promising results prompted a new COG pilot study of adding anti-GD2 to upfront chemotherapy in newly diagnosed patients with high-risk neuroblastoma, which was launched in December 2018. Meanwhile, Dr. Yu's group have generated preclinical data showing that combination of anti-GD2 with DFMO, an inhibitor of ornithine decarboxylase, not only dampened the undesirable neuropathic pain associated with anti-GD2, but also enhanced the anti-cancer efficacy of anti-GD2. These preclinical findings are being translated into clinical development.

In addition to ch14.18, a series of sequential phase II studies of a murine anti-GD2, mAb3F8 showed efficacy in neuroblastoma with an overall 5-year EFS of 62% for stage 4 patients in first remission who received 3F8 + GM-CSF + cis-retinoic acid. Recently, both ch14.18 and 3F8 have been humanized to Hu14.18 and Hu3F8 respectively. A phase I clinical trial of Hu14.18 showed that the maximum tolerated dose of hu14.18 to be 60

mg/m<sup>2</sup>/d for 4 days. A pilot study of hu14.18 in combination with 2 courses of chemotherapy in patients with newly diagnosed high risk neuroblastoma had generated impressive 76% PR or better responses in 42 patients (ASCO, 2017). Phase I study of Hu3F8 is ongoing.

There are several other anti-GD2 based immunotherapeutic strategies. A fusion protein of hu14.18 and IL-2, hu14.18-IL2 has been evaluated in a phase II study, which showed CR (5/23) for patients with disease evaluable by MIBG imaging and/or bone marrow histology, but no responses for patients with measurable disease. Several GD2-targeting bispecific antibodies have been generated and evaluated preclinically, and a phase I study of Hu3F8-BsAb is ongoing. Moreover, phase I clinical trials of various constructs for generation of GD2 directed CAR T have shown the feasibility and some anti-tumor efficacy of such cell therapy.

Furthermore, several GD2 specific vaccines including synthetic GD2 glycan, GD2-mimetic peptides and GD2-directed anti-idiotypic antibody have been generated to induce endogenous anti-GD2 responses. Some of these vaccines have undergone preclinical/clinical trials with documented safety and immune responses. However, their efficacy awaits further clinical evaluation.

# Treatment of High-Risk Neuroblastoma

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The prognosis of low- or intermediate-risk neuroblastoma is favorable; however, it has been unsatisfactory in high-risk neuroblastoma. Although the outcome of high-risk neuroblastoma has improved after the introduction of high-dose chemotherapy and autologous stem cell transplantation (HDCT/auto-SCT), the outcome after single HDCT/auto-SCT was unsatisfactory. The main cause of treatment failure after single HDCT/auto-SCT is relapse or tumor progression rather than treatment-related mortality (TRM). In this context, the role of tandem HDCT/auto-SCT has been investigated with the hypothesis that a sequential course of HDCT/auto-SCT might further improve the survival of high-risk neuroblastoma and encouraging survival rates have been reported. However, many patients still experienced tumor relapse or progression after the tandem HDCT/auto-SCT, particularly poor responders following induction therapy. Most relapsed patients experienced metastatic relapse and these findings suggest that further improvements in treatment need to be focused on systemic tumor control for high-risk neuroblastoma patients. Anti-GD2 treatment after tandem HDCT/auto-SCT could be one of the options to further improve the outcome for high-risk neuroblastoma patients. In a recent phase III randomized clinical trial of tandem versus single HDCT/auto-SCT by the Children's Oncology Group, the 3-year EFS was reported to be 73.7% in patients who received tandem HDCT/auto-SCT and post-consolidative immunotherapy. Cellular immunotherapy such as adoptive transfer of chimeric antigen receptors (CAR) of T cells or NK cells could also be considered. A combination of these immunotherapies following tandem HDCT/auto-SCT might further improve outcomes of high-risk neuroblastoma. It is well known that the genetic characteristics of neuroblastoma are important for predicting the treatment outcome and therefore are incorporated into the current risk-stratification system of neuroblastoma. Furthermore, recent studies suggest that germline characteristics of patients also affect the treatment outcome and toxicities during and after the treatment. Therefore, precision medicine based on both somatic and germline genomic characteristics might improve the outcome by minimizing the TRM and relapse rates.





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# Controversy on HSCT



# Novel Strategies to Prevent Relapse following Allogeneic Transplantation

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Relapse remains the most common reason for failure of allogeneic transplantation in patients with myeloid malignancies. Additionally, the rise of reduced conditioning intensity has contributed to the increased risk of post-transplant relapse. A randomized trial comparing high dose (MAC) to low dose (RIC) conditioning showed a higher rate of relapse in patients with acute myeloid leukemia (AML) who receive RIC. Therefore, preventive strategies are needed to reduce the risk of relapse which do not necessarily contribute to the risk of treatment related mortality from the conditioning regimen. A series of 3 pivotal phase 3 randomized trials have been performed evaluating the use of FLT3+ inhibitors and hypomethylating agents post-transplant in an effort to reduce relapse risk. The RADIUS trial a phase 2 randomized trial showed improved relapse-free survival (RFS) with maintenance midostaurin in patients with first CR FLT3+ AML who underwent MAC allogeneic transplant. Similarly, the SORMAIN trial a phase 3 randomized trial in patients with FLT3+ AML showed improved RFS in patients who underwent allogeneic transplant. A phase 3 randomized trial evaluating the use of maintenance azacitidine in patients with myelodysplastic syndrome (MDS) or AML showed no difference in RFS or overall survival. We will review the results of these studies and how they impact current transplant strategies. We will also review an ongoing BMT CTN trial evaluating gilteritinib for post-transplant maintenance in AML FLT3+ patients. The advent of targeted agents will hopefully fulfill the promise of post-transplant maintenance as a strategy to reduce relapse.



toxicities, less compromised performance status, superior response in poor cytogenetics, and availability of the outpatient regimen, pre-transplant hypomethylating treatment (HMT) are regarded as an attractive bridge. Several recent reports suggested that pre-transplant HMT could be used as a bridging therapy by stabilizing the disease or reducing tumor burden, especially for high-risk MDS. However, the selection of hypomethylating agents or treatment duration on an individual basis is still to be determined.

In this discussion, influences upon post-transplant MDS relapse of clinical factors, genetic mutations, WT1-based MRD assessment, and bridging treatment with HMA will be presented.

# Upfront auto-SCT for Peripheral T-cell Lymphoma: Is It Necessary?

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The PARMA study established the role of high dose chemotherapy and autologous peripheral stem cell transplant (HDC & APSCT) in relapsed refractory B-cell lymphomas. Given the poor outcomes of T-cell lymphomas, this option was explored in T-cell lymphomas. Retrospective studies as well as uncontrolled phase 2 studies suggest that upfront APSCT in T-cell lymphoma is feasible and seem to suggest a better outcome compared to historical controls. Consistently, these studies showed that achieving complete remission (CR) before APSCT was a strong predictor of improved survival in this stud. However, there has been no randomized comparison between upfront HDC & APSCT and conventional chemotherapy. Nonetheless, despite the absence of randomized trials, HDC & APSCT in first clinical remission (CR1) has been incorporated into guidelines. More recently, emerging data from Europe and Asia such as those from the LYSA suggest that consolidation APSCT at CR1 did not improve survival outcomes at least for patients with peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma and ALK-negative anaplastic large cell lymphoma. Survival of patients with aggressive T-cell lymphoma subtypes such as gamma delta T-cell and enteropathic T-cell lymphoma are universally poor even with high dose chemotherapy. This session reviews the controversies surrounding the role of upfront HDC and APSCT in patients with T-cell lymphoma attaining CR1 with conventional induction chemotherapy.

# Radiotherapy vs. High Dose Chemotherapy and Autologous Stem Cell Transplantation as Consolidation Therapy for Primary CNS Lymphoma

**Dok Hyun Yoon**

Asan Medical Center, University of Ulsan College of Medicine, Korea

Despite recent progress, the optimal therapeutic strategy for primary CNS lymphoma is still under investigation. While high-dose methotrexate-based induction chemotherapy, with high response rates and improved survival, has become cornerstone of treatment, consolidation therapy to improve long-term disease control and cure after the induction chemotherapy remains controversial. Whole brain radiotherapy (WBRT) has been the most widely accepted approach after induction chemotherapy. However, WBRT encompass inherent limitations in several aspects: inadequate local control of disease with in-field recurrence; leptomeningeal spread of lymphoma along spinal cord, outside of the radiation field; and irreversible neurotoxicity.<sup>1</sup> Especially late neurotoxicity causing decreased cognitive functions and memory deterioration is a significant concern to employ WBRT as consolidation approach. As an alternative, high-dose chemotherapy and autologous stem cell transplantation (ASCT) has been investigated and has shown efficacy and feasibility in several trials. Among various conditioning regimens, thiotepa-based regimens has shown encouraging outcomes, possibly due to high blood-brain-barrier permeability related to small size and lipophilic nature. However, thiotepa-based high dose therapy and ASCT is associated with significant hematologic and nonhematologic toxicities including very high rate of febrile neutropenia, grade 3-4 infections, gastrointestinal toxicities including high grade nausea/vomiting and mucositis, and higher rate of treatment-related mortalities compared with other conditioning regimen-based ASCT requiring expertise in the treatment. Even in those experienced centers, the approach is still limited by high medical resource requirement and prolonged hospitalization.

Two randomized phase 2 trials, IELSG32 and PRECIS, involving both consolidation approaches have been published in recent years.<sup>2,3</sup> Both trials have shown that both WBRT and thiotepa-based high dose therapy followed by ASCT are feasible and effective as consolidation after high dose methotrexate based induction chemotherapy with similar progression-free survival and overall survival rates. Neuropsychological tests suggest a potential impairment of cognitive functions after WBRT while neurocognitive functions have mostly improved or preserved after ASCT. ASCT arm experienced higher rates of grade 3 or 4 toxicities as expected with higher rates of treatment-related mortality. However, comparison of two approaches is limited as those trials are not prospectively designed to compare the outcomes. Considerations of the pro and cons in each



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# Nursing Symposium



# Investigation and Analysis of Venous Access in Hematopoietic Stem Cell Transplantation in China

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**Purpose:** To investigate the use of vein passage, to understand the problems in the use of CVC catheters in the field of hematopoietic stem cell transplantation in China through questionnaires.

**Method:** Issue electronic questionnaires, collect questionnaires and conduct data statistics.

**Results:** The survey collected questionnaires from 43 medical centers. In 2018, 4761 cases were transplanted, including 165 cases using infusion port, 2221 cases using PICC and 2375 cases using CVC catheter. There is no uniform retention time for CVC. The shortest retention time is 2d-52d and the longest retention time is 21d-180d; Among 31 medical centers using CVC catheter, 23 medical centers used dilute heparin to seal the CVC catheter, The concentration of dilute heparin was 10u/ml-100u/ml, The remaining 7 medical centers only used normal saline to seal the CVC catheter, The annual rate of occlusion of CVC catheter was 0-40%,It was most common in medical centers using NS to seal the CVC catheter; There were 64 cases of puncture point infection and 17 cases of catheter-related infection in 2375 cases of CVC catheter, all point infection cases were not treated with chlorhexidine gel patch, while 5 of 17 patients who had catheter-related infections were treated with chlorhexidine gel; In 8 hospitals, intravenous nutrition was not transfused through a single pathway; In 7 hospitals, needle-free transfusion was not used; In 2375 cases, 173 cases of CVC catheter (MARSI) occurred; In 2375 cases, 16 cases of catheter slippage, The reasons were inappropriate fixation in 5 cases, artificial extubation in 8 cases (such as resistance therapy, unconsciousness, etc.), postural change in 2 cases, and unidentified slippage in 1 case.

**Conclusion:** Consider the patient's needs and catheter condition to decision on CVC catheter retention time; Use Needle-free joints、Passive disinfection cap containing disinfectant and Chlorhexidine impregnated dressings to reduce puncture point infection and CVC catheter-related infection; In order to reduce the incidence of embolism, the tip of catheter should be located at CAJ point, use correct flushing and sealing procedures,when use two or more drugs, check the risk of precipitation ,if the risk is high flushing between drugs; There was no significant difference between different sealing solutions, guidelines recommend NS or 10u/ml dilute heparin solution for tube closure; In order to promote skin integrity, reduce complications and ease of use,it is necessary to select appropriate methods to fix venous catheters. There is insufficient evidence to prove which method is the best.

**Keywords:** hematopoietic stem cell transplantation, vein passage , CVC catheters, questionnaires

# Infection Control Using an Infection Control Best Practice Program

**Kumiko Takasaka**

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Infection control in HSCT in Japan is conducted at each medical institution by reference to the guidelines for early infection control after hematopoietic cell transplantation developed by the Japan Society for Hematopoietic Cell Transplantation. However, if the manual is not followed by everyone, the infection control will fail. We would like to introduce infection control using the infection control best practice "saizen", which is a program covering facets from manual development to confirmation of manual compliance, so that everyone can comply with the manual.

In the infection control best practice "saizen", clinical practitioners schematize the actual procedures, and then they consider if the procedures are evidence-based ones, and consider and decide the evidence-based procedures amongst themselves to schematize a new manual. And then, after colleagues are given training on the grounds and procedures of the new manual, they will start using the new manual. The subsequent status of compliance will be observed by others. Feedback on the observation results will be provided in the program, leading to improvement in the quality of infection control.

Case 1: Since it took time and there was variability in the operation, we undertook this for effective environmental management. To carry out cleaning from around the patient, and then from a high place to a low place, and from a clean place to an unclean place, the manual was created using photographs to show an effective method so that everyone can carry out cleaning using the same method. It reduced the time and enabled reliable environmental management by the standardized method.

Case 2: As infection frequently occurred in patients using PICC, manual development and direct observation were conducted, and the effectiveness was evaluated by surveillance. Infections decreased with improvement in the compliance rate.

# Infection Control Guidelines including Central Venous Catheter and Environmental Management in Seoul National University Hospital

**Mijeong Park**

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Data from the Korea Bone Marrow Transplant Nurses Society indicate that the first allogeneic bone marrow transplant began in 1983 in Korea and it increased gradually, approximately 33,885 HSCTs were performed in South Korea during 2018.

Since HSCT requires the recipient's bone marrow to be ablated, controlling infections before engraftment is an important task. The two main topics that will be covered are the proper handling of the patient's central venous catheters, and the proper management of the patient's environmental setting, which includes the room itself and the people and things that go in.

This presentation will share the guidelines and practices of HSCT for infection control in South Korea.

# Infection Control and Management of Environment- CVC Management. Clean Room Management

Rohani Binte Salleh

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## Abstract (Management of Clean Room)

In this discussion, we describe the importance of cleaning of the physical environment in health care settings as it relates to the prevention and control of infections.

The role in the management of cleaning/housekeeping services for the health care setting includes administrators, supervisors of Housekeeping Departments, Infection Prevention and Control professionals, supervisors of construction/maintenance projects and nurses.

In management of clean rooms, Infection Prevention and Control practices reinforce the following practices. To understand the principles of cleaning and disinfecting environmental surfaces, Infection transmission risk assessment to guide level of cleaning, cleaning practices for different types of care areas, including specialized cleaning for antibiotic-resistant microorganisms, frequency of cleaning, cleaning strategies for spills of blood and body substances, cleaning practices for non-critical equipment and furnishings, Handling of laundry and bedding, cleaning practices during and following completion of construction projects.

Environmental contamination may contribute to transmission of infections when healthcare workers contaminate their hands or gloves by touching contaminated surfaces, or when patients come into direct contact with contaminated surfaces. Scientific evidence suggests that environmental contamination plays an important role in the spread of MRSA and VRE, e.g., admitting a new patient to a room previously occupied by a MRSA- or VRE-positive patient significantly increases the risk of acquisition for MRSA or VRE. Outbreaks have been brought under control with infection control measures that include enhanced cleaning. One of Singapore General Hospital initiatives is to cohort patients with MRSA or VRE positive patients within 24 hours of their admission

Infection control aspects in housekeeping practices are important factors contributing to a safe and healthy environment in the hospital as well as at home. Although hand hygiene is important to minimize the impact of transmission of infections, cleaning and disinfecting of environmental surfaces is fundamental in reducing their potential contribution to the incidence of healthcare-associated infections. Routine cleaning is necessary to maintain a high standard of cleanliness at all times.

The selection of an ideal disinfectant usually depends on its effectiveness in destroying a specific organism. Studies have also shown that the human factor, frequency and duration of cleaning respectively also played a vital role in the entire cleaning process.

## **Abstract (Management of Central Venous Catheter)**

In managing Central Venous Catheter (CVC), improving patient's outcome and to reduce healthcare costs, it is the highest priority to be patient's advocates in reducing the incidence of catheter-related bloodstream infections (CRBSI). This is multidisciplinary efforts, involving healthcare professionals who order the insertion and removal of CVCs, those personnel who insert and maintain intravascular catheters, infection control nurses, healthcare staff managing the patients and patients who are capable of assisting in the care of their catheters. These infections independently increase hospital costs and length of stay.

The goal of an effective prevention program should be the elimination of CRBSI from all patient-care areas. Although this is challenging, programs have demonstrated success, but sustained elimination requires continued effort. The continue effort to educate healthcare personnel regarding the indications for intravascular catheter use, proper procedures for the insertion and maintenance of intravascular catheters, and appropriate infection control measures to prevent intravascular catheter-related infections. Designate only trained personnel who demonstrate competence for the insertion and maintenance of peripheral and central intravascular catheters. Yearly competency to assess staff knowledge and adherence to guidelines is very crucial.

These factors could contribute in best and effective management of CVC. They are to weigh the risks and benefits of placing a central venous device at a recommended site to reduce infectious complications against the risk for mechanical complications (e.g., pneumothorax, subclavian artery puncture, subclavian vein laceration, subclavian vein stenosis, hemothorax, thrombosis, air embolism, and catheter misplacement), to avoid using the femoral vein for central venous access in adult patients, use a subclavian site, rather than a jugular or a femoral site, in adult patients to minimize infection risk for non-tunneled CVC placement , use ultrasound guidance to place central venous catheters to reduce the number of cannulation attempts and mechanical complications. Promptly remove any intravascular catheter that is no longer essential.

Hand hygiene and aseptic technique either by washing hands with conventional soap and water or with alcohol-based hand rubs is another important factor in best practices in managing CVC. Hand hygiene should be performed before and after inserting, replacing, accessing and dressing an intravascular catheter

For Catheter Site Dressing Regimens we use sterile, transparent, semipermeable dressing to cover the catheter site and if the site is bleeding or oozing, use a gauze dressing until this is resolved. To replace catheter site dressing if the dressing becomes damp, loosened, or visibly soiled. Change dressings at least every 7 days for transparent dressings. Transparent, semi-permeable polyurethane dressings permit continuous visual inspection of the catheter site and require less frequent changes than the standard gauze and tape dressings. Monitor the catheter sites visually when changing the dressing or by palpation through an intact dressing on a regular basis, depending on the clinical situation of the individual patient. If patients have tenderness at the insertion site, fever without obvious source, or other manifestations suggesting local or bloodstream infection, the dressing should be removed to allow thorough examination of the site. Encourage patients to report any changes in their catheter site or any new discomfort.

Use of needleless connectors or mechanical valves appears to be effective in reducing connector colonization when compared with stopcocks and caps. In one study, the incidence of CRBSI was reduced when the



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needleless connector was compared with standard stopcocks. Appropriate disinfectants must be used to prevent transmission of microbes through connectors.

In addition, the time spent applying the disinfectant may be important. One study found that swiping the luer-activated device with 70% alcohol for only 3 to 5 seconds did not adequately disinfect the septal surface. In SGH, we swab the connector for at least 10 seconds.

Well-organized programs that enable healthcare providers to become educated and to provide, monitor, and evaluate care are critical to the success of this effort.

# Reducing Infection Density of Central Catheter-associated Bloodstream Infections due to Gram-Positive Cocci in the Hematology

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**Background:** For patients with hematologic malignancies, central venous catheter-related bloodstream infection is a fatal complication and have significant impacts on mortality and morbidity, increases in the length of hospital stay. The almost infection sites are related to hygiene, and the best results can be seen.

**Purposes:** This project aimed to examine the effects of using 2% Chlorhexidine Gluconate (CHG) bathing & dressing to reduce the infection density of central venous catheter (CVC)-associated bloodstream infections (BSI) due to Gram-Positive Cocci (GPC) in hematology patients.

**Method:** The BSI density of GPC rose from 1.9‰ in 2013. The risk factor analysis revealed that this deterioration may be caused by (1) compliance failure to skin-cleansing guidelines, (2) unawareness of the importance of skin-cleansing before and during CVC insertion, and (3) inability to provide the 2% CHG antiseptic solutions for daily skin-cleansing purposes. We executed the following measures: (1) formulation of the skin-cleansing guidelines, (2) training courses to educate nursing staff on the skin-cleansing techniques around CVC sites, (3) health-education leaflets and posters focusing on nursing skills for skin-cleansing, (4) daily use of antimicrobial solutions cleaning and weekly change dressing with CHG during admitted.

**Result:** The BSI density of GPC dropped to average 1.1‰ in 2014~2016 and continued to drop to average 0.48‰ during 2017 and June 2019.

**Conclusion:** By encouraging the nursing staff to provide professional instruction on proper skin-cleansing around the CVC sites and by raising the patient awareness of the importance of skin-cleansing and the actual implementation, we have successfully reduced the density of CVC associated Gram-positive cocci bloodstream infections. We also recommend this approach to other institutions.

# Establishment and Application of Continuous Nursing Model for Hematopoietic Stem Cell Transplantation Patients Based on Health System Model

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**Objective** To establish a long-term follow-up model with the medical team as the core of nurses as the leading factor based on Health System Model.

**Method** Cluster sampling is used to study the patients receiving hematopoietic stem cell transplantation in laminar flow ward of Peking University People's Hospital. Inclusion criteria were: 18-65 years old patients, and voluntary participation in the study. This study adopts a prospective research method, and based on Neuman Health System Model, emphasizes the four core concepts of "human, environment, health and nursing". Determine the continuing nursing process and content: This study refers to the following evidence-based basis and determines the follow-up frequency as 1 month, 3 months, 6 months and 12 months after transplantation. With the further development of the study, the follow-up time will probably continue to prolong, which will help to grasp more relevant data of long-term survival of HSCT patients. Specific research programs: The research includes post-transplant treatment, related nursing, post-transplant complications (infection, GVHD, relapse, etc.) related nursing, self-care guidance of patients and their families, psychological support, exercise intervention, etc. Interview with medical and nursing specialists in the field of HSCT: Experts are invited to make comments and suggestions on the continuing nursing process and content from different angles of doctors and nurses, especially for the treatment and nursing characteristics of Chinese HSCT patients. Design and complete the case report form (CRF) for HSCT patients, include :Karnofsky Functional State Score (KPS)、Functional Assessment of Cancer Treatment-Bone Marrow Transplant (FACT-BMT)、Functional Assessment of Chronic Disease Therapy-Fatigue Scale (FACIT-Fatigue)、Hospital Anxiety and Depression Scale (HAD)、Family Function Assessment Scale (APGAR)、Objective data: anthropometric data, complications, laboratory test data.

**Result** KPS, the KPS score is the lowest before transplantation, rising at 1 month after transplantation, declining at 3 months, and then rising significantly at 6 months after transplantation. obviously higher at 12 months after transplantation than that at 6 months after transplantation. FACT-BMT, At 1 month after transplantation, the FACT-BMT score is the lowest and the quality of life was the worst; then it begin to rise at 3 months after transplantation, at 12 months after transplantation, the KPS score is significantly higher than

that at 6 months. FACIT-Fatigue, it is the heaviest at 1 month after transplantation, and the fatigue score after transplantation is on the rise, and the fatigue score at 3 months after transplantation is significantly higher than that at 1 month. The fatigue score at 12 months after transplantation is significantly higher than that at 6 months after transplantation ; HAD, the anxiety score of HSCT patients is the highest in one month after transplantation, and then begins to decrease, especially at 6 months after transplantation, the score is significantly lower than that at three months; APGAR, the family function score of HSCT patients is the highest at one month after transplantation, and the family function score after transplantation shows a downward trend, and the family function score of 12 months after transplantation is significantly lower than that at 6 months after transplantation.

**Conclusion** According to multi-center research, based on the comprehensive evaluation of the continuous care platform, strengthen the information communication between the transplant hospital and the hospital where the patient lives, increase the accessibility of the patient after the transplant, and provide strong data and information support. At the same time, we will train a team of specialist nurses who can provide long-term continuous care for HSCT patients, improve the scientific research ability of clinical nurses, and thus promote the clinical transformation and application of scientific research results.

# Nationwide Survey on Long-Term Follow-Up Clinics after Hematopoietic Cell Transplantation in Japan

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## Introduction:

In recent years, over 3,500 allogeneic hematopoietic cell transplants (allo-HCT) are performed every year in Japan. Assuming that the two-year survival rate is around 60% after allo-HCT, over 2000 long-term survivors are estimated to increase annually. Since the medical insurance started to cover the cost of Long-term Follow-up (LTFU) Clinics after HCT in 2012, the number of hospitals that started LTFU clinics has been increasing. However, LTFU clinics are operated in different ways at different institutions. In order to characterize the current operation of LTFU clinics in Japan, we conducted a nationwide survey.

## Methods:

A questionnaire was sent to 189 hospitals conducting allo-HCT for adult patients. Questions and answer options were formed based on results from a previous qualitative survey by interviews with 10 hospitals that have operated LTFU clinics.

## Result:

140 (74%) hospitals responded to the survey. Ninety-six hospitals (69%) reported that they already had LTFU clinics, and the remaining 44 reported that they did not. Initiation of the LTFU clinics occurred most frequently (34%) in 2012 when the medical insurance started to cover the cost. 75% of hospitals answered that they saw all patients who received allo-HCT, and most frequent follow-up points were annual visits, followed by 6- and 3-month visits after HCT. The number of nurses who had completed the LTFU training program was 5 at a median and 19 at a maximum at each hospital. At the time of the survey, the number of nurses in charge of LTFU was 3 at a median and 11 at a maximum. The most common reason why trained nurses left LTFU service was department transfer within the institution (n=59). Other medical professionals involved with LTFU clinics were pharmacists and registered dietitians, with 60% of each being involved only when there are relevant issues. 65% of hospitals indicated that they would recommend patients to visit the LTFU clinics beyond 5 years after transplantation. Frequently used tools at LTFU clinics were medical interview sheets (84%), a passbook for allo-HCT recipients (72%), and brochures about daily life after allo-HCT (71%). We also assessed the free comments regarding challenges in the establishment and operation of LTFU clinics and found that major challenges were lack of labor, lack of cooperation and information sharing, and low consultation rates due to lack of understanding of the significance of LTFU clinics.

## Conclusion:

Tools, information resources, and human resource development need to be improved in order to promote effective and efficient LTFU.

# Self-Management at Home after Discharge of Hematopoietic Stem Cell Transplant Patients

**Gayeon Kim**

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Adult patients with various hematologic diseases such as leukemia, myelodysplastic syndrome, aplastic anemia, lymphoma, multiple myeloma, etc., plan hematopoietic stem cell transplantation for the purpose of cure. It is the treatment process of the transplant ward to perform conditioning chemotherapy and after hemocyte reduced stage and then patients discharged when they recovery. At this time, the patients are admitted to a cleanroom that is isolated from the external environment to reduce the extraneous infection resulting from the hospital environment. During the first month after transplantation, the patient is on the state of vulnerable to infectious diseases due to prolonged neutropenia, conditioning chemotherapy, and weakening of the mucosal barrier due to central venous catheter. During this period, they are living in a protective isolation unit and get professional infection control under the care of the medical staff. However, as discharged get closer the patient and the caregiver are afraid of self-management and infection control at home. With the steady increase in the number of transplant recipients, the need for and importance of selfcare after discharge of transplant patients are being emphasized. Standardized education is provided according to the CDC guideline at each hospital. In our hospital, main caregiver of patients is educated by professional nurses and dieticians about post-discharge life management. In addition, the transplant ward nurses have provided their own education for self-management after discharge from the ward. Education consists of five main themes: immunosuppressive medication, home environment management, daily life management, medical care, nutrition and diet.

The stages of opportunistic infections after hematopoietic stem cell transplantation (HSCT) are largely divided into phase I (pre-engraftment), phase II (post-engraftment), and phase III (late phase). Phase I (pre-engraftment) is susceptible to infection due to the reduction of neutrophils, which are the primary defenses, and various bacterial, fungal and viral infections may occur. In phase II (post-engraftment), CMV is reactivated, acute GvHD and steroid use may cause aspergillosis, and hemorrhagic cystitis may be caused by adenovirus and polyoma virus infection. Phase III (late) may cause respiratory virus infection due to seasonal changes and infections in the community, and reactivation of varicella zoster virus may cause shingles.

Thus, it is important to improve the level of self-management of patients and caregivers through post-discharge education because the degree of self-care affects infected patients who are exposed to various infection opportunities after transplantation.

# Follow up Management and Nursing Care of Survivor after BMT

**Jordan Hwang Chung Cheng**

Singapore General Hospital, Singapore

Haematopoietic stem cell transplantation provides an opportunity for patients with selected blood cancers the chance of a cure. Pre-stem cell transplantation treatment and conditioning treatment regimens during stem cell transplantation put stem cell transplant survivors at increased risks of late treatment-related complications. These survivors are also faced with hastened age-related physiological complications as compared to the general population. The post stem cell transplant long term follow up service in Singapore General Hospital will be discussed in this talk.

# The Effect of Long-Term Follow Up Clinic for Hematopoietic Stem Cell Transplantation Survivors in Taiwan

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## Background

Because of expanding indications and improvements in supportive care, the utilization of hematopoietic stem cell transplantation (HSCT) to treat various conditions is increasing exponentially. As the majority of survivors now live beyond the first 2 years after HSCT, they are prone to a unique set of complications and late effects. Until recently, HSCT experts assumed responsibility for almost all of the care for these survivors, but now oncologists/hematologists, and pediatricians, are involved frequently in offering specialized care and preventive services to these survivors. To integrate and translate into clinical practice the unique HSCT survivorship issues with current preventive guidelines, a team effort is required. This can be facilitated by a dedicated "long-term-follow-up (LTFU)" clinic that provides lifelong care for HSCT survivors.

## Methods

We built up our LTFU clinic models in 2012. The team members including infection physician, oncologists/hematologists, pediatricians, pharmacist, dietitians, psychiatrists and nurses. Our patient start their follow up program from preparing HSCT to long term follow up. Infection physician is responsible for LTFU clinic. Every patient visit LTFU clinic before their primary care physician clinic. We do patient education and physical exam to screen the long term complications( including acute chronic GVHD). LTFU clinic will give primary care physician suggestions according the assessment findings.

Every patients has their profile in HSCT management system in the computer. Every health care provider can research the data from preparing to long term follow up to trace the condition for every patients.

## Result

There were 680 allogeneic and 405 autologous HSCT patients visited LTFU clinic from 2012 to 2014. 30% of patients fatigue score were more than 4 (score 0~10). 26% of patients had moderate pain score. 14% patients had distress thermometer (DT) score more than 4(score 0~10). 13% of allogeneic HSCT patients had skin GVHD. 48% of allogeneic HSCT patients had chronic GVHD in eyes and 29% in lung and oral. We find the survivors had physical and phyco-social issues in LTFU. The care manager will tail the intervention and education for individual survivors including following the effect for the treatment and coordinating the team member for dealing the problem. We found three positive effects when we implanted LTFU clinic. First, We can find out problems earlier. When nurse practitioner do physical exam, they will take history comprehensively. Oncologists/hematologists can make decision on the basis of the nurse practitioner medical note, outpatient



nursing assessment sheet and patient self-reported questionnaire for GVHD. Second, we can do patient education in our LTFU clinic to improve their self-care efficacy. In addition, patients and their family can share their experiences when waiting for the clinic. Third, to decrease the patient readmission rate and improve the quality of life for the long term survivors.

### **Conclusion**

Our findings suggest HSCT survivors need LTFU clinic to assess HSCT survivors specific physical and mental problems. Survivors with risk factors for distress and physical problem difficult to return normal life might benefit from interventions and education in LTFU clinic. According to the result, we suggest care manager and LTFU clinic will be cost effective to long term HSCT survivors

# Laboratory Tests and Interpretation for HSCT

**Hyun Ji Lee**

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HLA disparity between hematopoietic stem cell donor and recipient triggers T-cell and NK cell allorecognition, and induces the GVHD. GVL effect may cause an engraftment failure. The HSCT from the alternative mismatched donor with one allele/antigen mismatch (9/10) can be as beneficial as a HSCT from a fully matched donor, especially in younger patients. The impacts of individual HLA locus mismatches on clinical outcomes of patients receiving unrelated-donor hematopoietic cell transplantation (HCT), as compared to HLA allele matched controls is controversial.

Analysis of chimerism following allogeneic stem cell transplantation has been a routine method for the assessment of engraftment and early detection of graft failure. Methods for monitoring of chimerism have also improved substantially; all techniques are established on the detection of genetic differences (polymorphisms) between recipient and donor. Multiplex short tandem repeat (STR) and polymerase chain reaction (PCR) is the most common method for the analysis of chimerism, due to the high informativity, feasibility, and high discrimination between donor and recipient. STRs or microsatellites are polymorphic genetic markers which have a repeat unit 4-bp to 6-bp long. Follow up of hematopoietic chimerism after allogeneic transplantation by STR is a useful tool for monitoring and determining the engraftment of donor cells and predicting the imminent relapse of the original disease.

In this session, the method of HLA typing and interpretation of high-resolution HLA results, and the method of STR will be reviewed, especially how to describe and report with case-based approach, mainly focused to interpret the result of STR reports.

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# Management of Chronic Graft-Versus-Host Disease (GVHD)

**Kwai Han Yoo**

Gachon University Gil Medical Center, Korea

Chronic graft-versus-host disease (GVHD) occurs in 30 to 70% of patients who have undergone allogeneic hematopoietic cell transplantation (HCT), and is the most relevant cause of late non-relapse morbidity and subsequent mortality (up to 30%).

The pathophysiology of chronic GVHD is mainly characterized by impaired immune tolerance mechanisms affecting innate and adaptive immunity. It is associated with B-cell signaling, naive T-cell differentiation into Th17, Tc17, Tfh and Tfr cells, and fibrosis-promoting factors. Risk factors for chronic GVHD are unrelated and/or mismatched donor, peripheral-blood stem-cell as donor source, older donor age, female donor into male recipient, and the use of total body irradiation, and the severity of acute GVHD.

Chronic GVHD usually begins between 3 months and 2 years after HCT. It can involve any organ systems, including oral, esophageal, musculoskeletal, joint, fascial, ocular, and lymphohematopoietic systems; hair and nails; and genital tissues. Chronic GVHD is diagnosed on the basis of symptoms of involved organs, laboratory values (for hepatic manifestations), and PFTs. The NIH consensus criteria provide a score for the severity of chronic GVHD. Eight organ systems (skin, mouth, eyes, gastrointestinal tract, liver, lungs, genital tract, and fasciae or joints) evaluated for diagnosis are scored individually for severity, and the individual scores are summed to calculate the overall severity of chronic GVHD.

The goal of GVHD treatment is the development of immunologic tolerance, indicated by successful withdrawal of all immunosuppressive treatment without recurrence or clinically significant exacerbation of disease manifestations. Optimal treatment of chronic GVHD requires a multidisciplinary team approach that includes transplantation specialists, a primary health care provider, organ-specific consultants, nurses, and ancillary services, and family support groups. First-line treatment consists of glucocorticoids given alone or in combination with calcineurin inhibitor (CNI). This achieves complete remission of chronic GVHD in approximately 20-50% of cases. If symptoms progress during the first 4 weeks of first-line therapy or there is no improvement in symptoms within 8–12 weeks, additional therapy should be initiated. Second-line treatments include mainly glucocorticoids and CNI, as well as immunomodulating therapies, and cytotoxic agents. Recently, ibrutinib (BTK inhibitor) was approved from the U.S. FDA for steroid-resistant GVHD. And several clinical trials with novel agents including SYK inhibitor, JAK1/2 inhibitor, ROCK2 inhibitor, and interleukin-6 inhibitor are also in progress. In addition to these treatments, supportive-care measures are essential for management of chronic GVHD.

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# Vaccination after HSCT

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Patients receiving hematopoietic stem cell transplantation (HSCT) are at risk for a number of infections that can be potentially preventive by vaccinations such as pneumococcal infections and influenza. Therefore, revaccination of HSCT recipients represents an important strategy for reducing morbidity and mortality associated with vaccine-preventable diseases. In this time, we will review the vaccination guidelines in HSCT recipients that have been published by major societies, and know which vaccines should not be missed to HSCT recipients.

# Nutritional Care in HSCT

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The nutritional management of patients with Hematopoietic cell transplantation (HCT) can be divided into the prevention of malnutrition and the prevention of infection.

As pre-transplantation nutritional status affects post-transplantation complications and outcomes, nutritional intervention is highly important before allogeneic HCT. Additionally, the conditioning regimen, including intensive chemotherapy and total body irradiation, may cause severe side effects, such as mucositis, nausea, vomiting, and diarrhea, resulting in the insufficient oral intake and extensive malabsorption and malnutrition via the gastrointestinal tract. Although nutritional support is an established part of supportive care prior to and during HCT, little is known about the long-term nutritional issues facing survivors. Also, more attention has recently been paid to the long-term management of HCT recipients, as malnutrition may significantly affect the clinical course and the patients' quality of life, even late after HCT. Thus, professional intervention by multidisciplinary nutritional support teams (NST) is indispensable in all processes of HCT.

HCT recipients' diet should be restricted prior to engraftment to decrease the risk of exposure to food-borne infections from bacteria, yeasts, molds, viruses, and parasites. Most cancer centers recommend the "neutropenic diet (low-microbial diet or low-bacterial diet)" for SCT recipients prior to engraftment. This diet should be continued for three months after autologous HCT, and allogeneic HCT recipients should remain on this diet until all immunosuppressive drugs are discontinued and the patient has reached the milestone of receiving live virus vaccines. However, the HCT physician should have final responsibility for determining when the diet can be discontinued safely. After querying 400 hospitals associated with the Association of Community Cancer Centers, Smith and Besser (2000) reported that 78% of the 156 responding hospitals used such a diet, typically once neutropenia ( $<1,000$  or  $1,500/\mu\text{L}$ ) was documented. The neutropenic diet has been part of the standard of care undergoing HCT for over 20 years. Although the practice to recommend this diet is endorsed by evidence-based guidelines, the quality of the evidence is generally weak, and clinical practices around the world vary. Additionally, there is a growing consensus that the neutropenic diet does not offer a protective effect against infection in patients undergoing HCT. The neutropenic diet eliminates food groups, putting patients at risk for nutritional deficiencies. Especially, pediatric HCT patients are at significant risk for developing food aversions and vitamin deficiencies since fruit and vegetable consumption are significantly reduced with the neutropenic diet. Therefore, the ASBMT guidelines for preventing infectious complications among HCT recipients (2009) emphasize that the potential benefit of food safety recommendations directed specifically toward HCT recipients must be weighed against the uncertain value of such recommendations and their potential to adversely affect patients' nutritional intake and/or quality of life.

In this session, I will provide a comprehensive overview of the current understanding of nutritional issues in patients with HCT.



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# General Lecture





# Something Fun through Beer

**Sang Joon Pae**

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Every alcoholic beverage has its own charm and personality. People have objective preconceptions about each drink and give subjective meaning. Whenever you drink a glass of champagne, you can remember the meaning of celebration, blessing, and drink a straight glass of whiskey, you will recall the warmth of the body in the cold winter. These cases are objective prejudices.

I am a beer lover. It was from medical school days. On Saturday afternoons, we used to play basketball until the end of the afternoon at dormitory grounds. After a shower in freezing cold water, we pounded into a pub in Sinchon, the exhilaration of 500cc of beer, which I had brought in at a time before I sat down, remained a vivid memory even after several decades. The subjective meaning of beer in my life will be "thrill" and "drinking with lots of friends" for the rest of my life. After being a surgeon, even after completing the surgery, drinking a glass of cold beer comes in the same impression as drinking a basketball or a shower after a medical school in my twenties.

Doctors often go abroad because there are many seminars. When I went to the US for participating in one seminar in 2007, I went to a small pub in the United States but, I couldn't read the beer list on the menu. (No matter how small the pub is, there are more than 10 basic beers available in the US.) I do not even know 30% of the thousands of American beer brands, but at that time, most Koreans, including me, were only separated from bottled beer and draft beer instead of IPA, Stout, Pilsner. Interpreting the beer menu plate was as difficult as interpreting Rosetta Stone. I have repeatedly said "Can you recommend the most delicious beer?" Throughout the trip, and I felt embarrassed when I came back to Korea. "Yes, if I study beer, I think I can drink all kinds of beer anywhere in the world." I bought and studied all the books related to beer.

After I learned about beer, traveling abroad made me twice as happy to eat food as the essential element of my trip. I am confident that teachers who enjoy a glass of beer will be able to enjoy the beer that they meet during their trips or conferences. If you enjoy eating, half of life is fun. I am going to fill up the lecture from now on in order to properly attach the item called beer which is indispensable to your life.



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# Student/Resident Lecture



# CAR-T Cell Therapy

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Recent several years, there have been observed the emergence of paradigm-shifting immunotherapeutic approaches in cancer treatment. One of the most promising modalities is a cellular therapy using genetically modified T cells to express a chimeric antigen receptor (CAR) effectively targeting tumor-specific antigens. CAR T cells can be generated by genetic modification of patient's T cells, following by ex vivo cell expansion. A CAR is composed of an antibody-derived single-chain variable fragment (scFv) responsible for antigen-recognition and an intracellular signaling domain of T cell receptor (TCR) which facilitates signal transduction to activate T cells during antigen recognition. Tumor-specificity of CARs can be induced in an HLA-independent manner. Costimulatory domains incorporated to intracellular domains of 2nd or 3rd generation CARs can enhance cytotoxicity, proliferation, persistence of CAR T cells. FDA approved CARs incorporate either CD28 or 4-1BB(CD137) as a costimulatory domain so far. The early clinical trials of CAR T cell therapy have been performed in patients with refractory lymphoid malignancies such as lymphoma and acute lymphoblastic leukemia with CTL019 targeting CD19 on tumor cells. Their feasible results have led further developments of other CAR T cells and clinical trials. In addition, early case reports showed the potential toxicities including off-target effect and cytokine release syndrome (CRS). CRS is a systemic inflammatory reaction induced by cytokines released by CAR T cells. CRS may result in severe organ dysfunctions or treatment-related mortality. CAR T cell therapy should be performed in an experienced institution according to the management guidelines for patients with CRS.

In this session, basic concept and development of CAR, its efficacy and safety would be discussed with highlighting key publications in the hematologic malignancies.

# Antibody Drugs for Hematological Cancers

**Yong Won Choi**

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Since Hybridoma technology was discovered in 1975, and Greg Winter pioneered the technique to humanize monoclonal antibodies (mAbs) in 1988, monoclonal antibodies have been successfully developed to treat medical illnesses. Monoclonal antibodies are effective treatments for inhibition of alloimmune reactivity, hematological malignancies, solid organ malignancies. Their successful use in cancer and autoimmune diseases in humans have made them one of the fastest growing classes of new drugs approved for these indications in last few decades. The first mAbs were derived from mice and provoked a strong immunological reaction when given to humans. The progress in genetic engineering allowed us to produce chimeric mAbs, consisting of 60 up to 90% of human antigens. Chimeric mAbs consist of human constant regions and mouse variable regions, responsible for the recognition of the antigen. Humanized antibodies contain up to 90% of human sequences. mAbs used in modern therapy are completely humanized and they contain only human amino acid sequences. mAbs destroy neoplastic cells by inducing apoptosis and blocking growth factor receptors or modulating their ligand-receptor interaction. In order to reach high therapeutic goals, mAbs are conjugated with radioisotopes, therapeutic goals, mAbs are conjugated with radioisotopes, toxins, cytostatics, or cytokines.

Rituximab is a chimeric mouse/human mAb therapy with binding specificity to CD20. It was the first therapeutic antibody approved for oncology patients. Since its initial approval in 1997, it has improved outcomes in all B-cell malignancies, including diffuse large B-cell lymphoma, follicular lymphoma, and chronic lymphocytic leukemia. Despite widespread use, most mechanistic data have been gathered from in vitro studies while the roles of the various response mechanisms in humans are still largely undetermined and no known biomarkers to indicate target engagement/tumor response have been identified, aside from reduced tumor burden. In the past decade, two new anti-CD20 antibodies have been approved: ofatumumab, which binds a distinct epitope of CD20, and obinutuzumab, derived from rituximab with modifications to the Fc portion and to its glycosylation.

Daratumumab is an IgG1k mAb directed against CD38. CD38 is overexpressed in multiple myeloma cells. Daratumumab binds to CD38, causing cells to apoptose via antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. Initial approval of daratumumab as monotherapy for patients with heavily pretreated multiple myeloma (MM) was based on the phase 1/2 GEN501 and SIRIUS trials. Subsequently, daratumumab in combination with standard-of-care therapy showed clinical benefit across phase 3 trials involving patients with newly diagnosed myeloma (the ALCYONE trial) and patients with relapsed or refractory MM (the CASTOR and POLLUX trials). In the POLLUX trial, treatment with daratumumab

plus lenalidomide and dexamethasone resulted in a risk of disease progression or death that was 63% lower than the risk with lenalidomide and dexamethasone alone. After a median follow-up of 44.3 months, the median progression-free survival was 44.5 months in the daratumumab group, as compared with 17.5 months in the control group, with no new safety concerns observed.

The signaling lymphocytic activation molecule family (SLAMF) of surface proteins is comprised of nine members, four of which are highly expressed on plasma cells from MM patients regardless of disease stage: SLAMF2 (CD48), SLAMF3 (CD229; Ly9), SLAMF6 (CD352), and SLAMF7 (CS1 or CD319). In November 2015 elotuzumab (HuLuc63), a humanized mAb that specifically binds to SLAMF7, received FDA approval for use in combination with lenalidomide and dexamethasone in MM patients who had received one to three previous drugs. Approval was based on the results of the phase III ELOQUENT-2 trial (NCT01239797) involving 646 RRMM patients randomly assigned to receive lenalidomide and dexamethasone with or without the mAb. The group receiving Elotuzumab demonstrated a reduced risk of disease progression (PFS: 19.4 vs. 14.9 months) and improved responses (ORR at one year: 68% vs. 57%; 41% vs. 27% at two years) compared to the control group. Recently published data from the Phase II ELOQUENT-3 trial (NCT02654132) reported gains in both PFS (10.3 vs. 4.7 months) and ORR (53% vs. 26%) when elotuzumab was added to a pomalidomide/dexamethasone regimen in 117 RRMM patients.

Antibody-drug conjugates (ADCs) are an emerging class of therapeutic agents that bring new opportunities for the treatment of hematological malignancies by meeting unmet medical needs. These drugs consist of a cytotoxic agent connected by a linker to a human, humanized, or chimeric antibody targeting a surface antigen specifically expressed by tumor cells.

Ibritumomab tiuxetan (Zevalin) is a monoclonal antibody radioimmunotherapy treatment for relapsed or refractory, low grade or transformed B cell non-Hodgkin's lymphoma, a lymphoproliferative disorder. The drug uses the monoclonal mouse IgG1 antibody ibritumomab in conjunction with the chelator tiuxetan, to which a radioactive isotope (either yttrium-90 or indium-111) is added.

Gemtuzumab Ozogamicin (Mylotarg) is a IgG4 recombinant humanized CD33 antibody conjugated to calicheamicin via an acid-labile hybrid 4-(4'-acetylphenoxy)butanoic acid linker. CD33 is a transmembrane glycoprotein which is highly expressed by bone marrow myeloid precursors in acute myeloid leukemia (AML). Gemtuzumab Ozogamicin was approved under an accelerated-approval process by the FDA in 2000 for use in patients over the age of 60 with relapsed acute myelogenous leukemia or those who are not considered candidates for standard chemotherapy. Within the first year after approval, the FDA required a black box warning be added to gemtuzumab packaging. The drug was noted to increase the risk of veno-occlusive disease (VOD) in the absence of bone marrow transplantation. Later the onset of VOD was shown to occur at increased frequency in gemtuzumab patients even following bone marrow transplantation. A randomized phase 3 comparative controlled trial (SWOG S0106) was initiated in 2004 by Wyeth in accordance with the FDA accelerated-approval process. The study was stopped prior to completion due to worrisome outcomes. Among the patients evaluated for early toxicity, fatal toxicity rate was significantly higher in the gemtuzumab combination therapy group vs the standard therapy group. Mortality was 5.7% with gemtuzumab and 1.4% without the agent (16/283 = 5.7% vs 4/281 = 1.4%; P = .01).



Brentuximab Vedotin (SGN-35) is an anti-CD30 antibody conjugated to monomethyl auristatin E (depolymerizing tubulin, thus blocking the cell cycle in G2/M) through a valine-citrulline peptide linker. In a pivotal phase II trial for patients with relapsed/refractory Hodgkin lymphoma (R/R HL), 75% of patients experienced an objective response. Among these, 34% were in complete remission (CR). Brentuximab Vedotin has demonstrated a clinical benefit as a maintenance treatment in preventing relapses after autologous stem cell transplantation (ASCT) in the phase III AETHERA trial and as a salvage therapy for HL patients in their first relapse or in progression. It, thereby, increases the chances of reaching a response and proceeding to transplant. A phase II study, which enrolled 58 R/R ALCL patients showed an 86% (n = 50) ORR, including 57% (n = 33) CR. Subsequently, accelerated approval of Brentuximab Vedotin by the FDA for the treatment of R/R HL and ALCL patients.

Nivolumab was tested in a phase I study that demonstrated objective responses in 20 of 23 heavily pretreated patients (87%) with relapsed/refractory cHL. Genetic alterations at 9p24.1 are almost universal in cHL, leading to overexpression of the programmed death 1 ligands 1 and 2 on the surface of tumor cells. On the basis of encouraging initial data, nivolumab was approved by FDA for the treatment of adults with R/R after auto-HCT and Brentuximab Vedotin treatment or three or more prior lines of systemic therapy including auto-HCT.

Blinatumomab has dual specificity for CD19 and CD3. It links T cells to target cells expressing CD19, a protein found on the majority of B-cell malignancies, causing redirected lysis of tumor cell. Blinatumomab was initially FDA approved in 2014 for treatment of Philadelphia chromosome (Ph)-negative relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL), based on the pivotal phase 2 trial by Topp and colleagues that demonstrated a CR rate of 43% in this patient population, with or without hematologic recovery. Further follow-up in a multicenter randomized phase 3 trial demonstrated significantly longer overall survival in patients treated with single-agent blinatumomab than among those treated with standard-of-care chemotherapy (7.7 months vs 4.0 months, P = .01). Remission rates were similar to the phase 2 trial, with CR/CRh of 43.9% within the first 2 cycles. As in the phase 2 trial, the majority of responders (76%) achieved MRD negativity, and a lower percentage of baseline bone marrow blasts was associated with increased CR/CRh (65% vs 34.4% for bone marrow blasts <50% or ≥50%, respectively). Subsequent trials in Ph+ and pediatric ALL demonstrated CR/CRh rates of 36% and 39%, respectively, leading to expansion of FDA approval for these indications in July 2017.

# Management of Hemophilia

**Sang Kyu Park**

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Hemophilia A (HA) and Hemophilia B (HB) are the most common severe bleeding disorders. Treatment has traditionally involved factor replacement therapy prophylactically and for bleeding episodes. Over the last 60 years, advances in protein purification, protein chemistry, donor screening, viral inactivation, gene sequencing, gene cloning, and recombinant protein production have dramatically enhanced the treatment and lives of patients with hemophilia. Recent efforts have produced enhanced half-life (EHL) clotting factors to better support prophylaxis and decrease the frequency of infusions. Medical needs remain in the areas of alternate modes of administration to decrease the need for venous access, better treatment, and prophylaxis for patients who form antibodies to clotting factors, and ultimately a cure of the underlying genetic defect. These advances, in combination with better diagnostics, are now enabling clinicians to improve the standard of care for people with hemophilia. Through this review we will discuss current plasma and recombinant FVIII (rFVIII) concentrates; provide an overview of recently approved EHL and newly developed FVIII concentrates; examine recently approved and developing nonfactor replacement options; and consider potential mechanisms for gene therapy.

# Thrombocytopenia in Hospitalized Patients

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Thrombocytopenia is common hematologic abnormality in hospitalized patients with various disease. In this case, some doctors may perform invasive test such as bone marrow examination regardless of the degree of thrombocytopenia. However, the incidence of thrombocytopenia due to hematologic malignancy is very rare. The etiology of thrombocytopenia in hospitalized patients is usually multifactorial and correcting one etiology may not normalize the low platelet count. Persisting thrombocytopenia can lead to fatal outcomes such as severe bleeding and death. Therefore, it is very important to identify the cause of thrombocytopenia as soon as possible. The mechanism of thrombocytopenia in hospitalized patients is explained by various causes as follows: increased platelet consumption (ex, disseminated intravascular coagulation), platelet aggregation or adherence to other cells (ex, sepsis or inflammatory disorders), increased destruction (ex, immune thrombocytopenia or drug induced), hemodilution (ex, administration of large amount fluids or blood products), splenic sequestration (ex, portal hypertension or hypersplenism), pseudothrombocytopenia (laboratory artifacts) and decreased platelet production (ex, bone marrow disorders or deficiency of vitamin B12 or folate).

There are several considerations to determine the cause of thrombocytopenia. First, the 'rapidity of development of thrombocytopenia' is very important. An acute decrease in platelet count can indicate an immune cause such as drug induced thrombocytopenia (D-ITP) or acute infection. 'Timing of onset of thrombocytopenia' also important. Thrombocytopenia that develops in the first 2–3 days of surgery or trauma is a response to the postoperative state or trauma. Thrombocytopenia that begins 5 or more days after receiving heparin should be considered heparin induced thrombocytopenia (HIT). The 'extent of thrombocytopenia' also provides an important clue to the cause. Acute drop in the count to  $<20 \times 10^9/L$  is uncommonly due to sepsis or DIC. In contrast, D-ITP usually causes platelet counts  $<20 \times 10^9/L$ , but severe thrombocytopenia is rare in patients with HIT. In patients with chronic kidney disease, thrombocytopenia is caused by multiple mechanisms, but may also be due to platelet adhesion to the dialysis-filtration membrane. In addition to the hemofilter membrane, thrombocytopenia may occur with a variety of artificial devices inserted into the body. Lastly, bone marrow disease also can be the cause of thrombocytopenia and can manifest in a variety of forms and degrees. Therefore, if unexplained thrombocytopenia persists, bone marrow examination should be considered.

In summary, thrombocytopenia in hospitalized patients is frequently seen with various severity and significance. Considering the multiple mechanism of thrombocytopenia, different treatment strategies are needed for individual patients. In addition, platelet transfusions should be considered only if the extent of thrombocytopenia is very severe or the symptoms of bleeding persist.

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# Case Discussion



# Who can Benefit from Allogeneic HSCT during Pediatric Leukemia Treatment in the NGS Era?

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Dramatic improvements in survival have been achieved in children and adolescents with acute lymphoblastic leukemia (ALL). The 5-year survival rate of ALL has increased to approximately 80~90% in this age group. Much of the improvement in survival is thought to be the effect of risk-based treatment. "Risk-based treatment" can be described as follows : Patients with various favorable clinical and biological factors who are likely to have a very good outcome receive modest therapy, and can be spared from more intensive and toxic treatment, while patients with unfavorable features and lower probability of long-term survival receive more aggressive, toxic therapeutic approach. Hence, assigning patients in proper risk groups is a key for successful treatment.

With clinical features at diagnosis and biologic characteristics of leukemia, early response to initial treatment is one of the three categories to define risk group in pediatric ALL. Early response to therapy is defined by minimal residual disease (MRD), and MRD is being measured with flowcytometry of detecting leukemia-specific cell surface markers, PCR assays, and next generation sequencing of unique clonality of B cell or T cell receptor. Most recently applied high-throughput sequencing method shows the sensitivity of MRD detection 1 in 1 million cells ( $10^{-6}$ ).

The more we sensitively detect remnant leukemia or growing leukemia cells in bone marrow, the more we might have to recheck treatment suitability of patients, change our treatment plan. In many treatment protocols, initial standard-risk group patients with high levels of postinduction MRD are recommended to augment their postinduction treatment as high-risk patients. However, patients initially assigned to high-risk or very high-risk group generally receive already intensified treatment, and augmenting therapy for high MRD can imply more toxic complication.

For either standard-risk or high-risk patients with continuous positive MRD detection, is there any role of allogeneic hematopoietic stem cell transplantation? And how much level of MRD positivity at the time of allogeneic hematopoietic stem cell transplantation affects the result of treatment outcome?

In the era of MRD with more sensitivity, there are many unknown answers of proper treatment modification and especially deciding transplantation for MRD positive patients. In this discussion session, debatable real patient cases will be presented, and recent updates about MRD in ALL and transplantation indication are going to be reviewed. We are waiting for your experience and good opinions. Hope to make a time to share recent updated knowledges.

# Best Donor Selection in Secondary Allogeneic Stem Cell Transplantation in Acute Leukemias

**Silvia Park**

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# Luncheon Symposium





# The Treatment of ITP with Romiplostim: Bringing New Data to Clinical Practice

**David J. Kuter, D.Phil.**

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USA

Immune thrombocytopenia (ITP) is a common autoimmune disease producing thrombocytopenia and an increased risk for bleeding. Less appreciated is that it is also associated with an increased risk of thrombosis and a marked increase in fatigue and reduced quality of life. While it affects patients of all ages, there is increased prevalence in children and in adults over age 65. While most children rapidly resolve this condition, many adults continue to have chronic thrombocytopenia.

For most patients the initial therapy is corticosteroids and if bleeding is severe sometimes intravenous immunoglobulin (IVIG). Most respond with a rise in platelets but many (>85% of adults) will relapse upon cessation of steroids and require further therapy. While splenectomy has historically been used in this setting, current guidelines discourage its early use and prefer medical therapy. Fortunately, a number of new treatments have emerged in recent years that have made medical therapy successful: rituximab, thrombopoietin-receptor agonists (TPO-RA; eg romiplostim, eltrombopag, avatrombopag, lusutrombopag), and fostamatinib. The new guidelines for ITP will emerge soon and will strongly favor the use of TPO-RA over rituximab with splenectomy being deferred for at least one year.

This lecture will review the use of romiplostim in the treatment of ITP and will focus on:

- romiplostim pathophysiology
- difference from the other TPO-RA
- new evidence for its efficacy earlier in the treatment of ITP
- predictors of response
- potential for remissions
- use in pediatric ITP
- recommendations on its clinical use

Romiplostim is a *peptibody* composed of four 14-amino acid peptides that bind the thrombopoietin (TPO) receptor.<sup>1</sup> It works identical to recombinant TPO and is highly potent in raising the platelet count in healthy subjects. It is 6-8 fold-more potent in raising the platelet count than eltrombopag<sup>2</sup> and it does not cause liver dysfunction. It has a half-life of 120-140 hours and is administered weekly by subcutaneous injection. Antibodies against it have rarely been reported but have not been clinically significant. It may be used in patients with renal and hepatic failure.

Initial studies showed responses in >80% of chronic ITP patients with a marked reduction in bleeding and

ability to discontinue other ITP treatments such as corticosteroids.<sup>3</sup> Later studies showed that most patients on it could avoid splenectomy<sup>4</sup> and had markedly improved health-related quality of life.<sup>5</sup> Romiplostim was more effective than rituximab in a retrospective analysis.<sup>6</sup> Over 5-10 years of treatment, there was no evidence for tachyphylaxis and platelet counts could be well maintained.<sup>7</sup>

Now after 11 years of experience with romiplostim, a number of aspects of romiplostim treatment have become clearer:

1. Although approved for "chronic" ITP, current data shows that romiplostim treatment is as effective in raising the platelet count and reducing bleeding in ITP that has not yet been chronic.<sup>8</sup> In a large analysis of ITP patients treated with romiplostim, responses were seen in 74% (204/277) of patients with ITP <1 year (many under 6 months) and in 71% (450/634) of those with ITP >1 year.
2. TPO levels may predict response.<sup>9</sup> Endogenous TPO levels are usually normal in patients with ITP but they may be used to predict who will NOT respond to TPO-RA. There is 82% (95% CI, 48%-98%) probability of non-response if TPO >209 pg/mL for romiplostim and an 82% (95% CI, 48%-98%) probability of non-response if TPO >136 pg/mL for eltrombopag; the difference probably reflecting the higher potency of romiplostim.
3. Romiplostim treatment may allow for ITP remissions to occur. In patients with ITP < 6 months, romiplostim treatment allowed 32% of patients to attain normal platelet counts and maintain them after treatment was stopped.<sup>10</sup> In a joint USA/Australian study, 28% of patients with chronic ITP treated with romiplostim for >6 months could come off therapy and maintain a hemostatic platelet count.<sup>11</sup>
4. Romiplostim is an effective treatment of pediatric ITP and is now FDA-approved for this indication. In one Phase III study, a platelet response was seen in 52% of patients treated with romiplostim versus 10% of those treated with standard of care.<sup>12</sup> In an open-label study of romiplostim in 65 children with ITP, nearly all patients (94%) had >1 platelet response (platelets >50x10<sup>9</sup>/L, no rescue medication in the prior 4 weeks), 72% responded at >75% of visits, and 58% responded at >90% of visits; 15 (23%) were able to discontinue therapy.<sup>13</sup>
5. Bone marrow fibrosis with romiplostim is not significant. A recent prospective bone marrow study of ITP patients on romiplostim<sup>14</sup> showed that only 5.3% and 1.5% showed increase in reticulin or collagen fibrosis, respectively. Most patients did not need to stop treatment but if stopped the fibrosis resolved. No patient developed a myeloproliferative disorder.
6. Compared with ITP patients treated with placebo, there was no increased rate of thrombosis.<sup>15</sup>

Key "tips" in using romiplostim in ITP are: begin at 3mcg/kg; target platelet count is 50-15x10<sup>9</sup>/L; don't miss a remission; if platelet count is >400x10<sup>9</sup>/L, don't hold a dose but reduce dose by 50-66%; remember that there is a great synergy between romiplostim and corticosteroids; changing dosing frequency is not a viable strategy and increases platelet fluctuation.

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# Current Status and Perspectives in the Treatment of Follicular Lymphoma

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In advanced stage follicular lymphoma (FL) substantial progress has been made in the last 10 to 15 years. The introduction of the CD 20 antibody Rituximab (Ritux) into FL therapy and its combination with chemotherapy has not only increased the response rates but also even prolonged overall survival. Hence, immunochemotherapy with Ritux plus CHOP, CVP or Bendamustine is the current standard in first line therapy of FL. The most promising perspectives for further improvements arise from novel antibodies and new agents. The most developed new anti CD 20 antibody is Obinutuzumab (Obi) which showed significant superiority over Ritux within the GALLIUM trial. A head to head comparison of Obi vs. Ritux and their combination with either Benda, CHOP or CVP revealed a significant prolongation of the progression-free survival (PFS) in roughly 1200 randomized patients. This was particularly relevant in patients with early progression (POD 24) or MRD or PET positivity at the end of induction. In an attempt to develop so called chemotherapy free therapies the combination of Ritux plus Lenalidomide ((Len) (R 2) was randomly compared to standard immunochemotherapy within the RELEVANCE trial. While no superiority was found for R 2 PFS was comparable so that R 2 may be considered as an alternative.

A large variety of different new agents are currently explored in FL therapy such as BTK inhibitors, PI3Kinase inhibitors, inhibitors of the bcl 2 pathway and several others. While the results of ongoing phase 2 and 3 studies must be awaited it seems justified to express the great hope that these new agents will improve the perspectives of FL patients further and may ultimately lead to more targeted approaches in FL treatment.

# Novel Prophylaxis Paradigm for CMV Management in Allo-HSCT Recipients

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Cytomegalovirus (CMV) infection has been historically one of the main threats to the success of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Over two decades ago, curtailment of CMV exposure and preemptive anti-CMV therapy reduced the occurrence of CMV disease and the rates of direct mortality associated with it. However, despite preemptive therapy, allo-HSCT recipients at risk for CMV infection and those who reactivate CMV after transplant have continued to suffer an increase indirect mortality of about 10-15% higher than seronegative allo-HSCT recipients not at risk of CMV infection. In addition, despite reduction in direct mortality and CMV disease, the occurrence of CMV infection and its required preemptive treatment associate with multiple forms of morbidity, side effects and with an increase use of resources for the health systems. Despite many additional efforts, including the development of newer diagnostic tests, new antivirals, anti-CMV vaccines and other developments, since the arrival of preemptive therapy, further substantial improvement in the outlook of CMV positive recipients of allo-HSCT remained elusive.

Letermovir is a first-in-class new antiviral drug which specifically blocks XXXXXXXX, and which in fase 2 and 3 registration trials of primary anti-CMV prophylaxis has shown for the first time to dramatically reduce the incidence of CMV infection and to significantly reduce patient mortality. This lecture will focus on the current paradigm and unmet needs of CMV management after allo-HSCT, on key letermovir mechanism of action and clinical trial data that support its approval and use for primary prophylaxis, and on the impact that letermovir will have on our CMV management protocols and on the outlook of real-world allo-HSCT recipients at risk for CMV infection. This lecture will be of interest to all hematologists and transplant physicians who manage allo-HSCT recipients at risk for CMV, to ID-specialists who support the management of these patients, and to Pharmacy and Drug Committees officials that would like to learn about this novel agent and its positioning in a novel prophylaxis paradigm for CMV management to the benefit of allo-HSCT candidates.

## **It's Time to Look beyond Immunosuppression** **- Recent Advances in Aplastic Anemia may Go Beyond Stem Cell Stimulation -**

**Phillip Scheinberg**

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The treatment for severe aplastic anemia (SAA) has evolved significantly in the last 10 years. Since the last 1970s SAA started to be recognized as an immune mediated diseases which responded to immunomodulatory drugs such as antithymocyte globulin (ATG) and cyclosporine (CsA). This represented a major advance in this deadly disease since blood counts were noted to recover weeks after the administration of this combination (ATG + CsA). Horse ATG was the formulation more widely used which received approval in the US for SAA. In the 1980s and 1990s laboratory experiments further advanced the notion of an immune pathogenesis mediated by TH-1 associated cytokines and proteins, a deficient regulatory T cell compartment, and oligoclonal T cell expansions which led the ultimate destruction of hematopoietic progenitor cells. With this regimen approximately 60-70% of patients were expected to recover their blood counts either partially (more often) or completely (less often). Importantly, recovery of blood counts associated with an improved survival long term. The problem of relapse in 1/3 of responders and late clonal evolution in 10-15% of all patients limited the success of this combination. Since the introduction of ATG +CsA in the late 1980s, progress in SAA became stagnant. Several efforts to improve outcomes were to no avail, unfortunately. More potent lymphocytotoxic therapies (rabbit ATG, alemtuzumab) were either inferior in outcome (compared to horse ATG) or prohibitively toxic (cyclophosphamide) and the addition of other immunosuppressants to horse ATG + CsA (MMF, sirolimus) not associated with better outcomes.

It wasn't until the early 2000s that a new approach of stimulating stem cells with the thrombopoietin receptor agonists did outcomes began to improve once again. Eltrombopag administered at high dose of 150 mg led to single and sometimes multilineage hematologic recoveries as single agent in patients who had failed initial ATG + CsA. Some of these responses were robust and durable which allowed for the discontinuation of eltrombopag in some cases. Clonal cytogenetic abnormalities, an initial concern with this regimen, to date has not produced a higher cumulative incidence of clonal evolution compared to what would be expected (historical comparison) in this patient population treated without eltrombopag. The next step of associating eltrombopag to upfront horse ATG + CsA produced the highest overall and complete response rate seen in SAA to date. This had led to an excellent survival outcome. Currently eltrombopag is approved in many countries as second line therapy in patients with an insufficient response to initial immunosuppression with approvals in first line being more recent in some countries. Interestingly, the initial mechanism of eltrombopag in stimulating stem cells may partially explain its activity in SAA. Alternative mechanisms of action have been shown in with eltrombopag in ITP that might be playing a role in SAA which includes immunomodulatory and tolerizing properties. Several of this aspects will be discussed in the talk at the meeting.

# Recent Advances of Treatment and Response Evaluation of Patients with Multiple Myeloma

**Kosei Matsue**

Kameda Medical Center

There have been many advances in understanding the pathophysiology and the disease evaluation of multiple myeloma (MM). Introduction of immunomodulatory drugs (IMiDs), and proteasome inhibitors (PIs) as well as the use of autologous stem cell transplantation have significantly contributed to the improvement the survival rate and quality of life of myeloma patients. The recent introduction of daratumumab, targeting a CD38 antigen on myeloma cells, has further allowed for the improvement of relapse/refractory patients with MM with or without the use of IMiDs or PIs. The mechanisms of daratumumab's actions include direct cell-mediated cytotoxicity, antibody-mediated cytotoxicity, and immunoregulatory mechanisms. We recently showed that blocking the suppressing immunoregulatory T cells might involve the efficacy of daratumumab in myeloma patients.

Despite these advances, not all patients benefit from these treatments. Various factors have been shown to affect the survival of patients. Among them, achieving a complete response (CR) or a very good partial response (VGPR) is associated with improved survival, and recent data have indicated that eradication of minimal residual disease (MRD) results in further stratification of the prognosis of patients among those with achieving CR or VGPR. MRD response reflects the individual tumor biology as well as the sensitivity to the agent used, therefore, suited for monitoring the response of the treatment. However, depth of IMWG treatment response, which largely rely on paraprotein production from tumorous plasma cells (PCs), may not always correctly reflect the residual PCs in the bone marrow because of heterogeneity of paraprotein production from tumorous PCs, especially after the use of novel agents. Considerable overlaps exist in the residual tumorous PCs levels among the IMWG responses. A combination of imaging modality with MRD assessment can further aids the assessment of treatment response. We recently showed that combination of PET-CT and quantitation of circulating tumorous PCs can stratified the prognosis of patients with MM.

In this session, I would like to introduce and discuss the recent treatment and response evaluation in patients with myeloma.



# How to Improve Survival Rates for Patients Undergoing HSCT: An Up to Date Approach to the Strategic Management of VOD/SOS

**Donal McLornan**

Consultant in Haemato-oncology and Stem Cell Transplantation

Hepatic veno-occlusive disease, also called sinusoidal obstruction syndrome (VOD/SOS), is a significant and potentially life-threatening complication that may arise following haematopoietic stem cell transplantation (HSCT) that requires pro-active clinician vigilance and prompt initiation of management. Incidence rates of VOD/SOS are variable, requiring adequate recognition, and dependant upon multiple factors including disease indication for transplant, pre-existing liver impairment, pre-transplant drug exposure and lines of therapy, gene polymorphisms, recipient age (children have higher incidence overall than adults), conditioning regimens (e.g. Total Body Irradiation use) and donor type amongst others<sup>1,2</sup>. Regarding VOD/SOS pathophysiology, sinusoidal endothelial cells and hepatocytes are damaged in zone 3 of the hepatic acinus. Sustained activation and subsequent damage of the sinusoidal endothelial cells may arise from multiple sources including toxic metabolites arising from conditioning therapies, pro-inflammatory cytokine storms, microbial product translocation via damaged mucosal barriers, calcineurin inhibitors and the engraftment process itself. Egress of red and white blood cells and cellular debris may move into the space of Disse, with the resultant dissected and sloughed endothelial cells moving downstream and causing sinusoidal flow obstruction. Moreover, there is upregulation of prothrombotic pathways and decreased fibrinolysis. Untreated, progressive post-sinusoidal hypertension may result, with increasing liver dysfunction, ascites, hepatorenal syndrome, encephalopathy and multi-organ failure<sup>1,2</sup>. Within this presentation, I will describe the common and less common clinical and laboratory findings associated with the onset and progression of VOD/SOS. Clinical presentations can differ significantly between the adult and paediatric populations and these will be highlighted<sup>1,3</sup>.

Most commonly, VOD/SOS presents within the first 21 days following HSCT but it is of extreme importance to note that late cases may arise, even after discharge, and in the current era may account for up to 15-20% of all VOD/SOS cases. Historically, both Baltimore and modified Seattle criteria are commonly used to aid the diagnosis but it is of note that these do not facilitate the diagnosis of late onset cases<sup>3</sup>. The revised EBMT criteria will be discussed in detail and importantly recognise both the classical form of VOD/SOS and this so-called late onset variant which is characterised as follows: Classical VOD/SOS picture beyond day 21: 1) Bilirubin  $\geq 2$  mg/dL and two of the following criteria: Painful hepatomegaly OR weight gain  $> 5\%$  OR ascites OR (2) Histologically proven VOD/SOS OR 3) Two or more of the following criteria: Bilirubin  $\geq 2$  mg/dL (or 34micromols/L) OR Painful hepatomegaly OR weight gain  $> 5\%$  OR ascites moreover, hemodynamical or/and

ultrasound evidence of VOD/SOS<sup>1</sup>. As can be seen, in these revised criteria hyper-bilirubinemia should no longer be mandatory for diagnosis for the late-onset variant.

As recognised by the global transplant community, the only curative proven licenced therapy for VOD/SOS is Defibrotide (Jazz Pharmaceuticals). It is apparent that multidisciplinary care is required for treatment success. Implementation of the proposed EBMT VOD/SOS criteria into routine clinical practice may well facilitate earlier intervention in patients requiring pre-emptive therapy with Defibrotide. Defibrotide possesses both antithrombotic and anti-inflammatory properties and has demonstrated significant reductions in VOD/SOS-related mortality and resolved VOD/SOS-related symptoms, with a manageable safety profile, in both clinical trials and in the 'real-world' setting<sup>2,4,5</sup>. Within this presentation, I will discuss mode of action of this agent, up-to-date trial data concerning defibrotide efficacy and safety and a practical approach to management of VOD/SOS as illustrated by recent clinical cases. Lastly, I will discuss potential biomarkers and novel predictors of response and how the diagnostic/ and both prophylactic and therapeutic field may evolve.

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# Feasible Outcome of Blinatumomab Followed by Allogeneic Hematopoietic Cell Transplantation for Adults With Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia at First Salvage

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In adult patients with B-cell precursor acute lymphoblastic leukemia (BCP-ALL), complete remission (CR) rates are 90% and long term overall survival (OS) is 30% to 60% after intensive chemotherapy with or without allogeneic hematopoietic cell transplantation (allo-HCT) (1-3). However, many patients with BCP-ALL relapse and die from leukemia progression. Relapse remains an unmet clinical challenge for physicians even after allo-HCT, which is the gold standard procedure for adult patients in first CR.

After relapse, CR rates are estimated to be much lower with the use of standard salvage chemotherapy, and survival outcomes are very poor (4-6). For safe salvage and bridge therapy to allo-HCT, several immune-based treatments such as bi-specific T-cell engager (BiTE) (7, 8), chimeric antigen receptor engineered T-cell therapy (CAR-T) (9), and antibody-drug conjugate platform have been attempted (10-12). More recently, the combination of immunotherapy with lower intensity cytotoxic therapy has been developed and provides very promising outcomes for the treatment of ALL (13-16).

Blinatumomab was the first BiTE antibody that demonstrated both a good safety profile and relevant antileukemic activity (17-21). Blinatumomab contains binding regions for the B-cell lineage specific CD19 and the invariant CD3 $\epsilon$  subunit of the T-cell receptor present on T lymphocytes, which is readily produced in high amounts with reliable purification and stability (22). The most rapid killing is mediated by perforin-granzyme activity of CD8<sup>+</sup> T-cells, but CD4<sup>+</sup> T-cells are also stimulated by blinatumomab (23). This novel drug is a powerful therapeutic option in patients with relapsed/refractory (R/R) BCP-ALL in major clinical trials, especially for patients treated earlier or those with minimal disease burden (17-20). However, remission rates, survival outcomes, and complications of this agent in real-world practice are not widely reported. The clinical effects of blinatumomab followed by allo-HCT as a first salvage treatment have yet to be elucidated, and the prognostic factors for blinatumomab response and survival outcome should be analyzed.

Recently, Catholic Hematology Hospital group reported treatment outcomes and prognostic factors for 32 adult patients with R/R Ph-negative BCP-ALL who received blinatumomab at first salvage. Patients who achieved CR proceeded to allogeneic hematopoietic cell transplantation (allo-HCT). At the time of blinatumomab treatment, 11 patients (34.3%) were primary refractory, 10 (31.4%) had relapsed with first CR

duration (CRD1)  $\geq 12$  months, and 11 (34.3%) had relapsed with CRD1  $< 12$  months. After the first blinatumomab cycle, 22 (68.8%) achieved CR. At the end of the second cycle, 20 of the 22 patients remained in persistent CR, and 1 patient achieved new CR. The overall minimal residual disease negativity rate was 75% among evaluable patients with persistent CR. Patients with CRD1  $< 12$  months were associated with poorer response to blinatumomab. Twenty (62.5%) of 32 patients underwent allo-HCT in blinatumomab-induced CR. After a median follow-up of 15.2 months, the 1-year OS rates for all patients and patients receiving allo-HCT in CR were 55.5% (median OS, 18.2 months) and 70.7%, respectively. Patients with CRD1  $< 12$  months, extramedullary disease (EMD), and high peripheral blood blasts were associated with poorer OS. Blinatumomab is effective for achieving good quality CR and bridging to allo-HCT for adult patients with R/R Ph-negative BCP-ALL in first salvage. The role of blinatumomab in patients with CRD1  $< 12$  months, EMD, or high tumor burden should be evaluated in future trials.

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# Ten Good Reasons to Use Anti-Thymocyte Globulin in the Conditioning Regimen

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Chronic GvHD remains a significant burden in patients undergoing an allogeneic hemopoietic stem cell transplantation (HSCT). The cumulative incidence of cGvHD has been increasing in the past years, due to the widespread use of peripheral blood (PB) as a stem cell source, and the greater use of donors other than HLA matched siblings.

In a prospective study, over 500 patients with cGvHD were registered and followed for events (Palmer et al, Haematologica 2015; 100: 690): 2 years after enrollment, 70% of the patients had either died, relapsed or had started a new systemic treatment, suggesting treatment failure. Therefore not only cGvHD is rather frequent, but is almost incurable.

**Reason 1.** Anti-thymocyte globulin (ATG) reduces the risk of moderate/severe cGvHD: this is shown by 5 randomized trials, including the risk of long term chronic lung dysfunction: this one shown in one randomized trial.

**Reason 2.** ATG increases the likelihood of being off immunosuppressive therapy one year post-transplant, as shown in one randomized trial, and improves the quality of life.

**Reason 3.** ATG reduces acute GvHD, shown in randomized studies as well as in meta-analyses.

**Reason 4.** ATG does not impair survival: all randomized trials have shown that patients receiving ATG or not, have comparable long term survival.

**Reason 5.** ATG does not increase the risk of relapse: this is perhaps the most important criticism of transplanters who refuse to use ATG, because of the fear that it will increase leukemia relapse. Again the randomized trials have shown this not to be the case.

**Reason 6.** ATG prevents GvHD but also rejection. In the early days ATG was used precisely with this aim, especially in combination with T cell depleted grafts in children with immunodeficiencies.

**Reason 7.** Because of reason 6, ATG should be considered always as a "must" in the conditioning regimen of patients with constitutional or acquired aplastic anemia. In these patients ATG provides a survival advantage.

**Reason 8.** ATG is relatively easy to use, and does not imply, expensive or sophisticated laboratory equipment to manipulate the stem cell graft.

**Reason 9.** ATG is a flexible agent, which can be used before the conditioning regimen (days -7-8), during the conditioning (days -3-2) and/or also after the transplant (day +7+9)

**Reason 10.** ATG can be combined with post-transplant cyclophosphamide (PT-CY) and has shown promising

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results in patients with non malignant diseases.

**Conclusions:** if you choose to use ATG, your patient will have the same probability of survival , but with a reduction of extensive cGvHD (from 41% to 12%), a reduction of chronic lung dysfunction (from 65% to 22%) , an increased probability of being off immunosuppressive therapy at 1 year (37% vs 16%) and improved quality of life.

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# Oral Presentation





OP-001

## LATE COMPLICATIONS AND QUALITY OF LIFE ASSESSMENT (FACT-BMT, HADS, NCCN DISTRESS THERMOMETER) FOR SURVIVORS AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION; TABLET-PC BASED SURVEYS

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**Background:** Allogeneic hematopoietic stem-cell transplantation (allo-HCT) is an only curative modality for hematologic malignancies. Allo-HCT, however, is physically and psychosocially demanding and can induce long term complications. Therefore, we aimed to investigate the unmet needs for physical and psychological late complications and clinical factors affecting the quality of life for allo-HCT survivors.

**Methods:** We retrospectively analyzed the survivorship clinic data including Tablet PC based-surveys of 69 adult allo-HCT survivors over two year post-transplant between 2015 and 2018 at Ulsan University Hospital, Ulsan, Korea.

**Result:** The median age was 46 years (range, 20-70). The most common symptom was fatigue (80.6%). The high risk patients for anxiety (HADS-A score  $\geq 8$ ) and depression (HADS-D score  $\geq 8$ ) was found in 14.9% and 13.6%, respectively. 10.4% of patients was in high distress status (NCCN DT score  $\geq 4$ ). We found that younger age ( $< 60$  years) was significantly associated with poor quality of life score (FACT-BMT) ( $P=0.001$ ) and high risk of fatigue ( $P=0.008$ ), anxiety (HADS-A) ( $P=0.001$ ), and depression (HADS-D) ( $P=0.025$ ). Female sex was significantly related to lower physical well-being score and higher distress score ( $P=0.046$  and  $P=0.05$ , respectively). Acute lymphoblast leukemia (ALL) survivors after allo-HCT showed significantly worse quality of life score (FACT-BMT) ( $P=0.006$ ) and higher depression score (HADS-D) ( $P=0.028$ ) compared to those with other disease. Chronic graft versus host disease (GVHD) and continuous immunosuppressant usage also have significant adverse impact on lower FACT-BMT score ( $P=0.024$  and  $P=0.033$ , respectively) and higher HADS-D score ( $P=0.015$  and  $P=0.019$ , respectively).

**Conclusion:** Allo-HCT survivors over 2 years following allo-HCT still have many physical and psychological symptoms. Younger patients ( $<60$  years), female, ALL, chronic GVHD, and sustained use of immunosuppressant were significant risk factors for worse quality of life and anxiety. We need to build more active survivorship care plan after allo-HCT especially for those patients.

**Keywords:** allogeneic hematopoietic cell transplantation, late complications, quality of life, FACT-BMT, HADS, distress

## POOLED ANALYSIS OF TIME TO COMPLETE RESPONSE AFTER DEFIBROTIDE INITIATION IN PATIENTS WITH HEPATIC VENO-OCCLUSIVE DISEASE/SINUSOIDAL OBSTRUCTION SYNDROME (VOD/SOS) AFTER HAEMATOPOIETIC CELL TRANSPLANTATION (HCT)

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**Background:** Defibrotide is approved for patients aged >1 month with severe hepatic VOD/SOS post-HCT in the EU, and for adult and paediatric patients with hepatic VOD/SOS with renal or pulmonary dysfunction post-HCT in the US and Canada. Defibrotide 25 mg/kg/day is recommended for  $\geq 21$  days and until signs and symptoms of VOD/SOS resolve. Time to complete response (CR), relative to defibrotide initiation, was evaluated in patients receiving defibrotide 25 mg/kg/day.

**Methods:** CR was defined as total serum bilirubin <2 mg/dL with resolution of VOD/SOS-related multi-organ dysfunction (MOD). Data were pooled from patients with VOD/SOS post-HCT treated with defibrotide in phase 2 (NCT00003966; n=74 receiving 25 mg/kg/day) and phase 3 (NCT00358501; n=102) studies. Duration of therapy in patients discontinuing due to CR in an expanded-access study (T-IND; NCT00628498; n=1,000) was analysed separately due to differences in response assessment.

**Results:** Pooled phase 2/3 studies had 60 patients with CR (n=34 [57%] and n=26 [43%], respectively); median time to CR was 24.5 days (range: 7–123). CR was achieved in 32/60 (53%) and 24/60 (40%) patients beyond 21 and 28 days of treatment, respectively. In T-IND, 390 patients discontinued due to CR (median time to discontinuation=22 days; range: 2–64); 235/390 (60%) and 57/390 (15%) patients discontinued beyond 21 and 28 days of treatment, respectively. In the phase 2/3 studies, 58/176 (33%) patients had treatment-related adverse events (TRAEs), most commonly ( $\geq 5\%$ ) hypotension (6%), pulmonary alveolar haemorrhage (6%), and epistaxis (5%). In T-IND, 210/1,000 (21%) patients had  $\geq 1$  TRAE, most commonly pulmonary haemorrhage (5%).

**Conclusions:** Overall, >50% of patients required defibrotide beyond 21 days to achieve CR; a notable proportion required treatment beyond 28 days, highlighting the importance of continuing defibrotide therapy until the signs and symptoms of VOD/SOS have resolved, which may occur beyond the recommended 21-day minimum indicated in the current labels.

**Keywords:** veno-occlusive disease (VOD), sinusoidal obstruction syndrome (SOS), defibrotide, complete response (CR), haematopoietic cell transplantation (HCT), efficacy

OP-003

## THE EFFECTS OF HORMONE THERAPY ON SERUM FOLLICLE-STIMULATING HORMONE, SERUM ESTRADIOL, AND BONE MASS FOLLOWING ALLOGENIC HEMATOPOIETIC CELL TRANSPLANTATION IN FEMALE PATIENTS OF CHILDBEARING AGE: SINGLE CENTER'S EXPERIENCE

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**Background:** Most female patients of childbearing age are exposed to premature ovarian failure after allogenic stem cell transplantation (SCT), which results in a decreased quality of life as well as an increased fracture risk due to bone loss. Based on the experience at a high-volume center, we analyzed how hormone therapy (HT) affects serum follicle-stimulating hormone (FSH) and estradiol levels and bone mineral density (BMD).

**Method:** Of 1,331 female patients who underwent allogenic SCT between March 2008 and April 2018 at our institution, those who not met for inclusion criteria (n=1,108) were excluded for the analysis. We finally retrospectively reviewed a total of 223 female patients of childbearing aged between 18 - 40 years.

**Results:** Among 223 patients, 170 (76.2%) patients received HT, and the mean time to commencement of HT after transplantation was  $15.1 \pm 8.2$  months. A significant increase in estradiol level was observed in patients receiving HT ( $p < 0.001$ ), but this increase was not different among 3 different types of HT regimen ( $p = 0.534$ ). The percent changes in BMD after 2 years of HT were significantly increased at all measurement sites: L-spine  $5.82 \pm 6.26\%$  ( $p < 0.001$ ), femoral neck  $3.36 \pm 17.78\%$  ( $p = 0.037$ ), total hip  $2.13 \pm 7.15\%$  ( $p = 0.001$ ). These changes were significant even with GVHD or with steroid exposure. However, there was no difference according to the HT regimen ( $p = 0.646$  for L-spine,  $p = 0.840$  for femoral neck, and  $p = 0.855$  for total hip).

**Conclusion:** HT in patients with premature ovarian failure following allogenic SCT effectively lowered serum FSH and increased serum estradiol levels. HT significantly increased BMD after the initiation of HT regardless of the history of GVHD or steroid exposure. These changes in hormones and BMD were observed regardless of the HT regimens.

**Keywords:** stem cell transplantation, follicle stimulating hormone, estradiol, bone density, hormone replacement therapy

## PRELIMINARY CLINICAL STUDY ON RISK SCORE AND STRATIFIED TREATMENT OF PRE-ENGRAFTMENT SYNDROME AFTER UNRELATED CORD BLOOD TRANSPLANTATION

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**Purpose or Background:** Pre-engraftment syndrome(PES) is a common immune reaction prior to neutrophil engraftment after unrelated cord blood transplantation (UCBT), with a unique clinical manifestation of non-infectious fever and skin rash. The reported incidence of PES ranges from 20% to 78%. Although many researchers believe that PES is associated with a high incidence of acute graft-versus-host disease(GVHD) but not with transplant-related mortality(TRM) , relapse, or overall survival(OS), they did not stratify the risk factors of PES.

**Methods:** First, 136 hematological malignancy patients treated with UCBT from April 2000 to February 2012 in our transplantation center were retrospectively analysis. Among them, 92 patients occurred PES. High-risk factors for 180-day TRM in PES patients were investigated by univariate and multivariate analysis. Then, from January 2013 to August 2016, 221 PES patients were scored according to the risk scoring system and stratified treated with different doses of methylprednisolone (MP)

**Results:** The cumulative incidence of neutrophil and platelet engraftment was significantly higher in PES group than non-PES group (97.8% vs.70.5%, $P<0.001$ ; 75.0% vs.54.5%, $P=0.05$ ). In 92 PES patients, multivariate analysis showed that failed MP treatment, multiple clinical symptoms and early onset of PES were independent risk factors affecting 180-day TRM. One risk factor was scored as 1. Then, from January 2013 to August 2016, 221 PES patients were scored according to high risk factors as PES-0, PES-1 and PES-2 and stratified treated with different doses of MP(0.5mg/kg/d for PES-0, 1mg/kg/d for PES-1 and 2mg/kg/d for PES-2). Compared with previous PES patients with the same score, the 180-day TRM of PES-1 and PES-2 patients was significantly reduced and the OS, LFS, and GRFS were significantly increased after stratified treatment.

**Conclusion:** PES after UCBT is benefit for engraftment, but should be graded according the risk scoring system. Different doses of MP stratified intervention therapy can significantly improve the prognosis of severe PES patients.

**Keywords:** Pre-engraftment syndrome, Unrelated cord blood transplantation, risk score, stratified treatment

OP-005

## POOR OUTCOME OF HLA-MISMATCHED ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN PATIENTS WITH ADVANCED MYELOFIBROSIS FOLLOWING REDUCED-INTENSITY CONDITIONING REGIMEN

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**Background:** Allogeneic-HCT is the only curative treatment for advanced myelofibrosis (MF). However, conditioning intensity, donor choice and GVHD prophylaxis strategies are not fully elucidated for better clinical outcomes.

**Methods:** We performed allogeneic-HCT for advanced MF with splenomegaly, refractory cytopenia, or leukemic transformation. From 2011 to 2018, 35 patients in intermediate-2 (n=10) to high-risk (n=25) based on DIPPS-plus treated with RIC-allo-HCT were analyzed. We firstly searched for MSD (n=15) followed by MUD (n=10), mismatched unrelated (n=5) and haploidentical donors (n=5). The conditioning regimen consisted of fludarabine (30 mg/m<sup>2</sup> for 5 days) and busulfan (3.2 mg/kg for 2 days) with TBI 200 to 400 cGy.

**Results:** There was one early graft failure (GF) and 2 leukemic relapse and 1 delayed GF. Two of them received DLI but progressed, and 1 died after 2nd allo-HCT. Improvement of BM fibrosis was observed in 29 (80.0%). After median follow-up of 24.6 months, 2-year OS was 57.8% and 2-year NRM was 29.9%. Acute GVHD was observed in 19 (6 grade-II, 8 grade-III, 4 grade-IV) and a cumulative incidence of grade III-IV acute GVHD was significantly higher in HLA-mismatched HCT (70% vs. 20%, p=0.008). Chronic GVHD was observed in 16 (5 mild, 7 moderate, 4 severe), and a cumulative incidence of severe chronic GVHD was relatively higher in HLA-mismatched HCT (30.0% vs. 8.0%, p=0.349). Significant hepatic GVHD was observed in 9 (5 acute, 4 chronic) and 6 of them died. Multivariate analysis revealed 2-year OS was significantly inferior in HLA-mismatched HCT (HR=7.11, 95%CI 2.0-24.8, p=0.002) and in patients with high ferritin>4000 ng/ml at post-HCT D+21 (HR=6.09, 95%CI 1.8-20.7, p=0.004) which showed more hepatic GVHD.

**Conclusion:** RIC-allo-HCT can be a valid choice for advanced MF patients. However, HLA-mismatched HCT and high post-HCT ferritin level related with hepatic GVHD should be regarded as poor predictive parameters for outcomes.

**Keywords :** myelofibrosis, allogeneic, hematopoietic cell transplantation, reduced intensity, GVHD

## DETECTING MANTLE CELL LYMPHOMA MINIMAL RESIDUAL DISEASE IN AUTOLOGOUS GRAFT THROUGH NEXT-GENERATION SEQUENCING AND THE IMPLICATION ON LONG-TERM REMISSION

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**Purpose:** Mantle cell lymphoma (MCL) patients typically present at an advanced stage. High-dose chemotherapy with autologous stem cell rescue (HDC-SCR) is the standard of care for eligible patients. Nevertheless, recurrence often intercedes in post-chemotherapy course. Minimal residual disease (MRD) had been proved to be predictive of relapse with worse overall survival (OS). This study employed next-generation sequencing (NGS) to optimize MRD identification for MCL and correlates its implications on post-HDC-SCR outcome.

**Method:** In this single-institute retrospective study, 112 MCL patients were recruited between 2006 and 2018. The median follow-up duration was 62 months. The median age at diagnosis was 62 years old. The Ann Arbor staging at diagnosis was mostly stage 4 (81.1 %). The blastoid variant comprised of 13.4%. Using MIPI scores, patients were stratified as low (27%), intermediate (34%), and high (39%) risk groups. In treatment, CHOP-like induction chemotherapy was given to 75% of this cohort. Forty patients received HDC-SCR while 6 patients received allogeneic transplant. We used LymphoTrack<sup>®</sup> Dx IGH/IGK assay coupled with Illumina MiSeq sequencer to analyze V(D)J recombination in the diagnostic formalin-fixed paraffin-embedded samples and autografts.

**Results:** The median OS was 95 months. Blastoid variant was associated with worse survival ( $p < 0.001$ ). Concerning pre-HDC-SCR disease status, patients achieved complete remission had better OS than those who did not ( $p = 0.042$ ). Twelve patients undertook NGS-based MRD analysis for their diagnostic and autograft paired samples. Six (50%) patients developed relapse. Four of these six patients were positive for NGS-based MRD in the autografts. Interestingly, the other two patients without NGS-based MRD in autografts developed recurrence from their pre-HDC-SCR FDG-PET lesions.

**Conclusion:** This study supports that HDC-SCR confers OS benefit. Autologous graft MRD detection by NGS analysis helps prediction of relapse. Meanwhile, for patients without MRD in autograft, post-HDC-SCR consolidative radiotherapy might help curb relapse and warrants further investigation.

**Keywords:** Mantle cell lymphoma, Minimal residual disease, Next-generation sequencing, Autologous graft, Relapse, Long-term remission

OP-007

## COMPARISON OF CONDITIONING REGIMENS IN PATIENTS WITH NATURAL KILLER/T-CELL LYMPHOMA UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANTATION: SINGLE-CENTER EXPERIENCE

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**Purpose or Background:** At present, autologous stem cell transplantation(ASCT) is recommended as consolidation therapy for natural killer/T-cell lymphoma(NKTCL) in most clinical guidelines. However, the optimal conditioning regimen has not been determined. In this study, we retrospectively analyzed three different conditioning regimens(busulfan-based, carmustine-based and gemcitabine-containing) in patients with NKTCL.

**Method or Case:** Between January 2002 and August 2018, fifty-six patients with advanced/relapsed/refractory NKTCL undergoing ASCT at the Sun Yat-sen University Cancer Center were reviewed. All patients achieved CR before ASCT. The conditioning regimens included: BuCyE(busulfan: 3.2 mg/kg D-6 to D-4, cyclophosphamide: 50mg/kg D-3 to D-2, etoposide: 200mg/m<sup>2</sup> D-6 to D-3), BEAM(carmustine: 300 mg/m<sup>2</sup> D-5, cytarabine: 200mg/m<sup>2</sup> D-5 to D-2, etoposide: 200 mg/m<sup>2</sup> D-5 to D-2, melphalan: 140 mg/m<sup>2</sup> D-2), and GemBuMel(gemcitabine: 1200 mg/m<sup>2</sup>, 2-hour infusion, D-7,D-3 ; busulfan: 2mg/kg D-7 to D-4, melphalan: 70 mg/m<sup>2</sup> D-3,D-2). The latest follow-up was updated to April 30th, 2019.

**Results or Progress:** Overall, four patients were excluded due to lost to follow-up. In the BuCyE group(n=23), the BEAM group(n=21), and the GemBuMel group(n=8), the results were as follows: the median age, the proportion of male, and the CD34 cell counts were of no difference in each groups. The median time to neutrophil recovery(>0.5\*10<sup>9</sup>/L)were 9 days, 9 days, and 11 days respectively, the median time to platelet recovery(>20\*10<sup>9</sup>/L) were 12 days, 12 days, and 15 days respectively. The major grade III/IV non-hematological toxicities included: oral mucositis(4%, 4%, 12.5%), diarrhea(4%, 9%, 25%), and infection(4%, 9%, 25%). The median follow-up time was 32 months(range, 3-192 months). The 2-year overall survival were 79.0%, 76.1%, and 50.0% respectively (P=0.062). The 2-year progression-free survival were 73.4%, 57.1%, and 37.5% respectively (P=0.247).

**Conclusion or Discussion:** Our study indicated that BEAM was comparable to BuCyE as conditioning regimen in NKTCL. Unfortunately, GemBuMel seemed to be associated with more adverse effects and poorer survival.

**Keywords:** autologous, conditioning regimen, natural killer/T-cell lymphoma, transplantation



## SIMILAR OUTCOME OF MANTLE CELL LYMPHOMA PATIENTS UNDERGOING EARLY OR LATE HEMATOPOIETIC STEM CELL TRANSPLANTATION -- ON BEHALF OF TAIWAN SOCIETY OF BLOOD AND MARROW TRANSPLANTATION REGISTRY

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**Purpose or Background:** Mantle cell lymphoma usually presented with advanced disease and difficult to cure after rituximab plus CHOP-like chemotherapy. After the introduction of more intensive upfront poly-chemotherapy and high dose chemotherapy plus autologous stem cell transplantation, the survival could be prolonged to six years or longer in transplant-eligible patients. We want to know in real world practice whether the difference of outcome is between early versus late transplantation in MCL patients.

**Method:** We collected patients undergoing hematopoietic stem cell transplantation from nationwide registered TSBMT data base. We analyzed the clinical presentation, pre-transplant disease status, time interval between diagnosis and transplantation, and transplant outcome of patients. The primary endpoint is overall survival and secondary endpoint is progression free survival and survival functions were estimated using Kaplan-Meier methodology with appropriate 95% Cis and according to different pre-transplant disease status.

**Results:** Forty-six patients underwent autologous and nine underwent allogeneic stem cell transplantations between Feb 2004 and Mar 2016 and median age at diagnosis was 54 with range 35 to 74. Fifty-three of them (97%) were advanced stage and 20% had extranodal disease. The disease status before transplantation were 28 (51%) in CR1, 8 (15%) in CR2, 18 (33%) in PR, and 1 (2%) in relapsed refractory. The median time interval between diagnosis and transplantation was 0.78 years with range 0.42 to 7.34 years. Three-year and five-year overall survival were 83% and 59% with longer survival in non-extra-nodal involvement patients. The progression free survival rate after HSCT were 42% and 19% in three and five years, respectively. There was no significant difference of overall survival between patients transplanted in CR1, CR2, or PR before transplantation.

**Conclusion or Discussion:** There was no significant difference of overall survival between patients of different disease status (CR vs PR) before transplantation and early vs late transplantation.

**Keywords:** mantle cell lymphoma, hematopoietic stem cell transplantation

OP-009

## IMPACT OF AUTOLOGOUS STEM CELL TRANSPLANTATION ON RENAL RESPONSE IN MULTIPLE MYELOMA PATIENTS WITH ADVANCED RENAL FAILURE

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**Purpose or Background:** This study aimed to evaluate the efficacy of autologous stem cell transplantation (ASCT) on renal outcomes of multiple myeloma (MM) patients who had renal impairment with estimated glomerular filtration rates (eGFR)  $\leq 60$  ml/min/1.73m<sup>2</sup> at the time point of transplantation

**Method or Case:** In our ASCT database from July 2009 to September 2018, 76 MM patients with median eGFR of 36.6 (range, 5.4-59.8) ml/min/1.73m<sup>2</sup> at ASCT were included: 47 (61.8%) with eGFR  $\geq 30$  and  $< 60$  ml/min/1.73m<sup>2</sup>; 16 (21.1%) with eGFR  $\geq 15$  and  $< 30$  ml/min/1.73m<sup>2</sup>; and 13 (16.9%) with eGFR  $< 15$  ml/min/1.73m<sup>2</sup> and/or hemodialysis-dependent. Myeloma and renal response after ASCT were evaluated using the international myeloma working group response criteria.

**Results or Progress:** During median follow-up of 37.3 (range 0.9-108.3) months, transplant-related mortality occurred in seven patients (9.1%). Overall myeloma response was achieved in 70 patients (92.1%): 6 (7.9%) of partial response (PR), 12 (15.8%) of very good partial response (VGPR), and 52 (68.4%) of complete response (CR). Median myeloma progression-free survival (PFS) and overall survival were 23.2 (95% CI, 16.9-32.1) and 61.5 (95% CI, 43.6-69.8) months, respectively. Among 20 patients (26.3%) who achieved renal response, including 19 (25.0%) of renal CR and 1 (1.3%) of renal PR, median time to achieve partial response was 267 days (range, 3-2022). In subgroup (n=29) with baseline eGFR  $< 30$  ml/min/1.73m<sup>2</sup>, 21 patients (53.8%) achieved renal response after median 53 (3-1756) days post ASCT. In multivariate analysis, IgA type, advanced eGFR ( $< 30$  ml/min/1.73m<sup>2</sup>), and shorter duration from diagnosis to ASCT ( $< 6.6$  months) were associated with higher cumulative rate for achieving renal response.

**Conclusion or Discussion:** Clinical outcome of myeloma patients after ASCT was favorable. Patients with advanced renal failure may benefit from early ASCT.

**Keywords:** Multiple myeloma, Renal impairment, ASCT

## DIFFERENT EFFECTS OF MINIMAL RESIDUAL DISEASE ON OUTCOMES OF PATIENTS WITH PHILADELPHIA CHROMOSOME-POSITIVE ALL WHO UNDERWENT HLA-MATCHED SIBLING DONOR TRANSPLANTATION AND THOSE RECEIVED HAPLOIDENTICAL ALLOGRAFTS

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**Purpose or Background:** This study compared the effects of pre-transplantation minimal residual disease (pre-MRD) on outcomes of patients with Ph+ ALL who underwent human leukocyte antigen-matched sibling donor transplantation (MSDT) and those received unmanipulated haploidentical SCT (haplo-SCT).

**Method or Case:** A total of 187 patients with Ph+ ALL who underwent MSDT (n=57) and unmanipulated haplo-SCT (n=130) were retrospectively included. MRD was detected by RQ-PCR.

**Results or Progress:** After a median follow up of 1005 days in total patient group, the 4-year cumulative incidence of relapse (CIR) and non-relapse mortality (NRM) were 17.1% and 14.7%, respectively. The 4-year probability of overall survival (OS) and leukemia-free survival (LFS) was 74.3% and 69.4%, respectively. Patients with positive pre-MRD had a higher 4-year CIR than those with negative one (25.8% vs. 13.9%, P=0.025), however, the NRM (8.5% vs. 16.7%, P=0.238), LFS (64.8% vs. 70.8%, P=0.375), and OS (69.1% vs. 76.0%, P=0.399) were comparable. In MSDT group, patients with positive pre-MRD had increased 4 year CIR (56.4% vs. 11.1%, P=0.002) and decreased 4-year OS (35.9% vs. 75.6%, P=0.02) and LFS (35.9% vs. 69.0%, P=0.041) than those with negative one. In haplo-SCT settings, the 4-year CIR (P=0.551), NRM (P=0.317) and the 4-year probability of OS (P=0.671), LFS (P=0.869) were comparable between the positive pre-MRD and negative pre-MRD groups. In subgroup patients with positive pre-MRD, haplo-SCT had a lower 4 year CIR (14.3% vs. 56.4%, P=0.027) and a higher 4-year LFS (76.5% vs. 35.9%, P=0.056) and OS (82.4% vs. 35.9%, P=0.020) than those of MSDT. Multivariate analysis showed that haplo-SCT was associated with low CIR (HR, 0.283; P=0.038) and superior OS (HR, 0.398; P=0.029) in cases with positive pre-MRD subgroup.

**Conclusion or Discussion:** The results indicate a different effect of pre-MRD on outcomes of patients who underwent haplo-SCT and those received MSDT, suggesting that haplo-SCT could have a stronger GVL compared with MSDT.

**Keywords:** Haploidentical allografts, Philadelphia-chromosome positive, acute lymphoblastic leukemia, HLA-matched sibling donor transplantation, minimal residual disease

OP-011

## A NOVEL TLR5 AGONIST PROTECTS INTESTINAL LGR5+ STEM CELLS THROUGH ACTIVATES HOST-DERIVED IL-22 IN GVHD

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**Background:** Graft-versus-host disease (GVHD) in the gastrointestinal (GI) tract remains a major cause of morbidity and mortality following allogeneic hematopoietic stem-cell transplantation (HSCT). Despite the fact that damage to intestinal stem cells (ISCs) and their niche cells in the GI tract plays a key role in amplifying systemic disease (GI GVHD), little is known about treatment strategies that can selectively regulate the ISC compartment. Here, we showed Toll-like receptors 5 (TLR5) as a crucial regulator of intestinal tissue sensitivity to GVHD and a protective factor for ISC during inflammatory intestinal injury.

**Method:** We established a complete MHC-mismatched C57BL/6 → BALB/c GVHD model and investigated the effects of a novel TLR5 agonist, KMRC011. KMRC011 is a derivative of Salmonella enterica flagellin and is designed by removing the N-terminal ancillary tail region of entolimod to function as an agonist of TLR5. Recipients were administered with KMRC011 by intraperitoneal injections at 2-day intervals from 1 day before BMT to 7 days after BMT. All animals were monitored for survival and clinical signs of GVHD.

**Results:** Administration of KMRC011 significantly attenuated the GVHD-related mortality and inhibited severe tissue damage in the intestine, liver and lung. In particular, our results demonstrate that KMRC011 directly targeted intestinal tissues and protected ISC from allogeneic immune-mediated tissue damage. These protective effects are correlated with the observed increase in IL-22 and IL-23 expression in the host intestinal tissues. In addition, KMRC011 did not induce Th17 and Th22 polarization from donor CD4+ T cells and inhibited subsequent pro-inflammatory cytokine cascades.

**Conclusion:** The present study suggested that a novel TLR5 agonist, KMRC011 could effectively prevent acute GVHD through protecting intestinal Lgr5+ stem cells in IL-22-dependent manner.

**Keywords:** Graft-versus-host disease, GVHD, Toll-like receptors 5, TLR5, intestinal stem cells, ISCs, Interleukin 22, IL-22

## VARIATIONS IN GUT MICROBIOTA AND FECAL METABOLIC PHENOTYPE ASSOCIATED WITH PMN-MDSCS BY 16S RRNA GENE SEQUENCING AND LC/MS-BASED METABOLOMICS IN MICE AGVHD

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**Background:** Acute graft-versus-host disease (aGVHD) is one of the fatal and refractory complications after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) as a major part of MDSCs play a role of immunosuppressive activity and balance immune homeostasis. While little research has regarded the relationship of PMN-MDSCs and alterations of intestinal microbiota and microbial metabolites in aGVHD.

**Method:** Non-aGVHD group, aGVHD group and PMN-MDSCs-depleted aGVHD group were established. We used an integrated approach of 16S rRNA gene sequencing combined with ultra-high-performance liquid chromatography-mass spectrometry (UHPLC-MS)-based metabolomics to analyze the gut microbiota and fecal metabolic phenotype.

**Results:** The PMN-MDSCs-depleted aGVHD group showed most severe aGVHD symptoms including rapid weight loss and shortened survival time. The relative abundance of Anaerotruncus increased in all aGVHD groups compared to non-aGVHD group, while Ruminococcaceae and Clostridium\_IV only decreased in PMN-MDSCs-depleted aGVHD group. Moreover, the PMN-MDSCs-depleted aGVHD group showed extremely low expression and loss of diversity of metabolites. Meanwhile, distinct changes in the fecal metabolic phenotype were found. Lipid and fatty acid biosynthesis such as Acyl carnitine, Rimexolone and Myricolal significantly decreased in all aGVHD groups. Compared to aGVHD group, Amino acid synthesis including Tyrosine, Asparagine, Histidine decreased in PMN-MDSCs-depleted aGVHD group. Furthermore, the data indicated that the gut microbes especially Firmicutes were potentially associated with the altered fecal metabolites.

**Conclusion or Discussion:** Our results indicate for the first time that donor bone marrow derived-PMN-MDSCs in allo-HSCT affect the diversity and abundance of gut microbiota and metabolomics in aGVHD.

**Keywords** PMN-MDSCs, aGVHD, gut microbiota, metabolomics, allo-HSCT

## POTENTIAL INFLUENCE OF HEMATOLOGICAL OR IMMUNOLOGICAL HEREDITARY PREDISPOSITION GENES ON OUTCOMES OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

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**Purpose or Background:** To investigate whether hematological and immunological hereditary predisposition genes have influence on outcomes of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in hematological malignancies.

**Method or Case:** Between January 2018 and March 2019, 77 patients with hematologic malignancies who underwent allo-HSCT were enrolled. Median age was 17 (1.8 to 53). Diagnosis included AML (n=24), ALL (n=45), and NHL (n=8). Disease status was CR1 in 28, CR2 in 38, PR in 3, and NR in 8. Donors were haploidentical family members (n=64) or identical siblings (n=4) or unrelated volunteers (n=9). The conditioning was myeloablative. GVHD prophylaxis was with cyclosporine, short-term MTX and mycophenolate mofetil. ATG was used in haploidentical and unrelated transplants. Prevention of Fungal, PCP and herpes virus infections was routinely applied. Next generation sequencing was used to detect hematological and immunological hereditary predisposition genes before transplant.

**Results or Progress:** Twenty-eight (36.4%) cases carried primary hemophagocytic syndrome (HLH) related genes, and average gene number was 1.2 (range 1-2); 37 (48.1%) cases carried Fanconi anemia related genes, and average gene number was 1.3 (range 1-3); 59 (76.6%) cases carried immunodeficiency related genes, and average gene number was 2.3 (range 1-6). The incidence of aGVHD in patients carried HLH genes was significant higher than that without HLH genes (42.9% vs. 20.4%,  $p=0.036$ ). Bacterial infections occurred more frequent in patients with Fanconi anemia genes than that without those genes (51.4% vs. 20.0%,  $p = 0.004$ ). There was a trend of higher relapse rate in patients with immunodeficiency related genes than that without those genes (14.5% vs. 5.56%,  $p > 0.05$ ), but without statistical significance.

**Conclusion or Discussion:** Our results indicate that hematological and immunological hereditary predisposition genes may have potential influence on outcomes of allo-HSCT in hematological malignancies, which include GVHD, infection and perhaps relapse as well. Larger cohort and longer follow-up are needed to address this issue.

**Keywords:** hereditary predisposition genes, hematological malignancies, hematopoietic stem cell transplantation, HSCT complications

## COMPARISON OF IMMUNOREGULATORY EFFECTS OF HUMAN MESENCHYMAL STEM CELLS DERIVED FROM UMBILICAL CORD AND BONE MARROW

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Mesenchymal stem cells (MSCs) have immunoregulatory properties that are valuable for cell therapy to treat graft-versus-host disease (GVHD). Until recently, human bone marrow-derived MSCs (BM-MSCs) were the most widely used MSCs in cell therapy, despite the invasive collection method and decrease in donors. Recently, MSCs derived from human umbilical cords (UC-MSCs) have gained popularity as cell therapy material for their ethical and non-invasive collection. We investigated the mechanisms of the immunosuppressive effects of UC-MSCs and BM-MSCs. We reconstituted inflammatory environments in vitro with combinations of interferon-gamma (IFN- $\gamma$ ), tumor necrosis factor alpha (TNF- $\alpha$ ), and interleukin 1 beta (IL-1 $\beta$ ), or with IFN- $\gamma$  alone. We analyzed soluble factors, such as indoleamine 2,3-dioxygenase (IDO), cyclooxygenase-2 (COX2), prostaglandin E2 (PGE2), and IL-6. BM-MSCs expressed more IDO after cytokine stimulation, and UC-MSCs secreted more PGE2 and IL-6 in the in vitro inflammatory environment. In addition, we cocultured activated T cells with MSCs treated with indomethacin and/or anti-IL-10 and observed that both COX2 and IL-10 were involved in the immunomodulatory mechanisms. To assess the ability of MSCs to inhibit T helper 17 (Th17) cells and induce regulatory T cells (Tregs), we induced Th17 cells and cocultured them with MSCs treated with indomethacin or anti-IL-10. UC-MSCs inhibited more Th17 cells and induced more Tregs than BM-MSCs. These findings suggest that UC-MSCs have distinct immunoregulatory functions and may substitute BM-MSCs in the field of cell therapy.

**Keywords:** Mesenchymal Stem Cells, Graft-versus-Host Disease, Cellular Therapy

OP-015

## ABNORMAL DIFFERENTIATION OF NESTIN+ MESENCHYMAL STEM CELLS IN PATIENTS WITH CHRONIC GRAFT-VERSUS-HOST DISEASE

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**Background:** Chronic graft-versus-host disease (cGVHD) is a major cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT). The roles of bone marrow niche in cGVHD pathogenesis have gained increasing attention in recent years. Nestin+ mesenchymal stem cells (MSCs) is an important component of bone marrow niche. However, the potential implication of Nestin+ MSCs in the pathophysiology of cGVHD has not been completely clarified.

**Method:** A total of 68 patients with hematologic malignancies who underwent allo-HSCT at Nanfang Hospital between April 2016 and October 2018 were enrolled in this experimental study. We analyzed expanded Nestin+ MSCs from patients with cGVHD and compared them with patients without cGVHD. The diagnosis and grade of cGVHD was made at the time of sample collection according to National Institutes of Health criteria (Howard M.S. et. al. BBMT 2015). The results were compared using one-way ANOVA and unpaired two-tailed Student t-test. Statistical significance was defined as P value of <0.05.

**Results:** The Nestin+ MSCs from both groups showed similar morphology, immunophenotype, proliferation, and apoptosis. However, the adipogenic differentiation capacity of Nestin+ MSCs in patients with cGVHD was significantly reduced compared with patients without cGVHD (relative expression of PPAR $\gamma$   $2.22\pm0.27$ , and  $6.82\pm0.87$ , respectively,  $P=0.01$ ). The osteogenic differentiation capacity was significantly increased in patients with cGVHD (relative expression of RUNX2  $3.84\pm0.38$ , and  $1.95\pm0.52$ , respectively,  $P=0.02$ ). These abnormal differentiations were more significant in patients with moderate/severe cGVHD. Furthermore,  $\beta$ -catenin phosphorylation decreased and nuclear  $\beta$ -catenin increased in the Nestin+ MSCs of cGVHD patients.

**Conclusion:** These results demonstrate that Nestin+ MSCs from cGVHD patients had abnormal differentiation characterized by decreased adipogenic differentiation capacity and enhanced osteogenic capacity. The reduction of phosphorylation of  $\beta$ -catenin play an important role in these abnormal differentiations.

**Keywords:** mesenchymal stem cell, hematopoietic stem cell transplantation, chronic graft-versus-host disease



## PREVALENCE AND RISK FACTORS OF HAVING ANTIBODIES TO CLASS I AND II HUMAN LEUKOCYTE ANTIGENS IN OLDER HAPLOIDENTICAL STEM CELL TRANSPLANTATION CANDIDATES

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**Purpose or Background:** The effect of donor-specific anti-human leukocyte antigen (HLA) antibodies (DSAs) has been recognized as a factor in graft failure (GF) in patients who underwent umbilical cord blood transplantation (UBT), matched unrelated donor transplantation (MUDT), or haploidentical stem cell transplantation (haplo-SCT). Presently, we know little about the prevalence of and risk factors for having anti-HLA antibodies among older transplant candidates.

**Method or Case:** Therefore, we analyzed 273 older patients with hematologic disease who were waiting for haplo-SCT.

**Results or Progress:** Among all patients, 73 (26.7%) patients had a positive panel-reactive antibody (PRA) result for class I, 38 (13.9%) for class II, and 32 (11.7%) for both. Multivariate analysis showed that females were at a higher risk for having a PRA result for class II ( $P=0.001$ ) and for having antibodies against HLA-C ( $P=0.003$ ) and HLA-DR ( $P=0.002$ ). Prior pregnancy was a risk factor for having a PRA result for class I ( $P<0.001$ ) and for having antibodies against HLA-A ( $P<0.001$ ), HLA-B ( $P<0.001$ ) and HLA-DQ ( $P=0.024$ ). Previous transfusion was a risk factor for the following: having a positive PRA result for class II ( $P<0.001$ ); having antibodies against HLA-A ( $p=0.045$ ), HLA-B ( $p=0.043$ ), HLA-DP ( $P<0.001$ ), HLA-DQ ( $P<0.001$ ), and HLA-DR ( $P<0.001$ ); and having higher numbers of antibodies to specific HLA loci ( $P=0.005$ ).

**Conclusion or Discussion:** Our findings indicated that female sex, prior pregnancy, and previous transfusion are independent risk factors for older patients with hematologic disease for having DSAs, which could guide anti-HLA antibody monitoring and be helpful for donor selection.

**Keywords:** Stem cell transplantation, Anti-HLA antibody, gender, pregnancy, transfusion

OP-017

## PROGNOSTIC GENETIC MUTATIONS IN PATIENTS WITH MYELOYDYSPLASTIC SYNDROME TREATED WITH HEMATOPOIETIC STEM-CELL TRANSPLANTATION

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**Purpose or Background:** Genetic mutations in myelodysplastic syndrome (MDS) patients are closely related with clinical phenotypes and prognosis in MDS patients. But whether mutations are prognostic for outcomes after allogeneic hematopoietic stem-cell transplantation(allo-HSCT) remains to be elaborated. This research was done to figure out whether genetic mutations help the risk-stratification in MDS patients received transplantation.

**Method or Case:** Targeted mutational analysis were performed on samples obtained before transplantation from 151 patients underwent HSCT. We analyzed the relationship of mutations and clinical outcomes. Uni- and multi-variate Cox models were used for the survival analysis. Clinical variables were induced to adjust the P value. Relapse in RAEB and sAML patients was defined when the percentage of bone marrow blasts above 5%. Cumulative incidence of relapse was assessed using the Fine-Gray model and compared by Grey-test, with non-relapse mortality as the competing factor.

**Results or Progress:** All 151 patients carried more than one somatic mutations, most frequently in DNAB2(47.02%), KDM6B (45.03%), USH2A (41.06%), KMT2D(99.07%). After adjusted by clinical features including bone marrow blasts, karyotype, HCT-CI, univariate Cox regression analyses revealed that mutations in FLT3 (hazard ratio [HR], 2.428; 95% Confidence Interval [95%CI], 1.134 to 5.200; P = 0.022) and PDGFRB (HR, 2.452; 95%CI, 1.000 to 6.009; P = 0.050) were associated with shorter overall survival. Multivariate Cox regression models confirmed that FLT3 (HR, 2.329; 95%CI, 1.075 to 5.042; P = 0.032) abnormality as an independent risk factor for patient death. Mutations in TP53 was associated with adverse karyotype. FLT3D7G mutation was associated with different relapse risk according to different VAF.

**Conclusion or Discussion:** FLT3 mutations is independently associated with shorter survival in MDS patients treated with allo-HSCT. Loss of heterogeneity of FLT3D7G may associated with higher risk of relapse after allo-HSCT.

**Keywords:** MDS, allo-HSCT, mutations, FLT3

## UP-REGULATION OF THE MIR-92A AND MIR-181A IN PATIENTS WITH ACUTE MYELOID LEUKEMIA AND THEIR INHIBITION WITH LOCKED NUCLEIC ACID (LNA)-ANTIMIRNA; INTRODUCING C-KIT AS A NEW TARGET GENE

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**Purpose or Background:** Dysregulated expression of various microRNAs (miRNAs) has been widely observed in hematopoietic malignancies like acute myeloid leukemia (AML). In this study, we evaluated the expression of the miR-92a and miR-181a in newly diagnosed AML patients compared to healthy controls

**Method or Case:** we investigated for the first time the effect of blocking of the miR-92a and miR181a on the expression of cKit, CEBPA and WT1 genes in HL-60 cell line. For evaluation of the relative gene expression, SYBR Green Real-Time PCR method was performed. The expression of miRNAs was inhibited by transfection of the HL-60 cell line with locked nucleic acid (LNA)anti-miRNA. The viability of transfected cells was evaluated by MTT assay

**Results or Progress:** Both miR-92a and miR-181a are highly overexpressed in AML patients compared to healthy controls. Also, miR181a expression was associated with poor prognosis of AML patients. The blockage of the miR92a and miR-181a remarkably reduces cell viability. In addition, inhibition of miR-92a with LNA-anti-miR-92a significantly decreased c-Kit level. Conversely, miR-181a blockage was associated with upregulated c-Kit expression. Taking together, miR-92a and miR-181a are dysregulated in AML patients and c-Kit gene might be a novel target for these miRNAs

**Conclusion or Discussion:** Regarding the anti-proliferative effect of LNA-anti-miR-92a and LNA-anti-miR-181a, regulation of miR-92a and miR-181a expression might be a useful approach in line with conventional chemotherapy to limit blast cell survival and reduce leukemic cell proliferation. Keywords: MicroRNA; Acute myeloid leukemia (AML); locked nucleic acid (LNA)-anti-miRNA; Gene expression

**Keywords:** MicroRNA, Acute myeloid leukemia

OP-019

## THE PREDICTIVE VALUE OF MINIMAL RESIDUAL DISEASE WHEN FACING THE INCONSISTENT RESULTS DETECTED BY REAL-TIME QUANTITATIVE PCR AND FLOW CYTOMETRY IN NPM1-MUTATED ACUTE MYELOID LEUKEMIA

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**Purpose or Background:** For acute myeloid leukemia (AML) with nucleophosmin 1 mutation (NPM1m), multiparameter flow cytometry (FCM) and real-time quantitative polymerase chain reaction (RQ-PCR) are used to monitor minimal residual disease (MRD). But sometimes results of the two methods are not consistent. This study was designed to analyze how to deal with the discordant results of FCM and RQ-PCR in AML chemotherapy patients, especially when positive FCM (FCM+) and negative NPM1m (NPM1m-) were detected in the same sample.

**Method or Case:** Our study included 93 AML patients with NPM1m (NPM1m+) who received chemotherapy but did not underwent hematopoietic stem cell transplantation. We monitored NPM1m and leukemia associated immunophenotypes (LAIP) by RQ-PCR and FCM, respectively, to assess MRD after each chemotherapy course. All patients were classified into four groups based on the results of FCM and RQ-PCR: with both negative (group 1: FCM-NPM1m-), with a single positive (group 2: FCM-NPM1m+, group 3: FCM+NPM1m-), with both positive (group 4: FCM+NPM1m+) after each course of chemotherapy.

**Results or Progress:** The results showed that patients between group 2 and group 3 had no significant difference in 2-year cumulative incidence of relapse (CIR) after each course of chemotherapy. Furthermore, patients of group 2 and group 3 had a lower 2-year CIR than that of group 4, and a significantly higher 2-year CIR than that of group 1 after the first two courses. The patients of group 1 had a significantly higher 2-year CIR than that of group 4 after remission induction of chemotherapy.

**Conclusion or Discussion:** These results suggested that in the MRD monitoring process of AML patients, when results of FCM and RQ-PCR were inconsistent, especially when FCM was positive and NPM1m was negative, these single positive results still had predictive significance for relapse.

**Keywords:** acute myeloid leukemia, minimal residual disease, NPM1 mutation, multiparameter flow cytometry

## IMPACT OF DELAYED COMPLETE REMISSION ON PROGNOSIS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR ACUTE MYELOID LEUKEMIA

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**Purpose or Background:** Many clinical parameters have been reported to have a prognostic impact on patients receiving hematopoietic stem cell transplantation (HSCT). However, literature about the outcome difference of HSCT for patients achieving complete remission after either one (early CR1) or two cycles (delayed CR1) of induction chemotherapy remains scarce.

**Methods:** Totally, 254 adult AML patients receiving allo-HSCT at CR1 or CR2 at NTUH between 1985 and 2015 were consecutively enrolled. We compared the clinical parameters and analyzed the survival data between patients with early CR1 (n=104, 40.9%), delayed CR1 (n=67, 26.4%), and CR2 (n=83, 32.7%).

**Results:** Among the groups of early CR1, delayed CR1, and CR2, there was no significant difference in gender, age, and white blood cell counts at diagnosis, and the proportion of secondary AML. These groups had similar rates of favorable, intermediate, and unfavorable-risk cytogenetics. The rates of harboring NPM1mutant, FLT3-ITD mutant, or NPM1mutant/FLT3-ITDWT were comparable. There were no differences in the conditioning regimens (myeloablative vs. reduced intensity) or stem cell sources.

With a median follow-up time of 75.9 months (range, 0.7-361.6), the 5-year relapse rate was much lower for patients with early CR1 than those with delayed CR1 or CR2 (21.9% vs. 38% vs. 47.0%,  $P=0.004$ ). The OS was also much longer for the patients with early CR1 than those with delayed CR1 or CR2 (median, not reached vs. 64.7 vs. 66.4 months,  $P=0.005$ ). Interestingly, there were no significant differences in OS and relapse rates between delay CR1 and CR2 groups ( $P=0.868$  and  $0.440$ , respectively).

In multivariate Cox proportional hazards regression analysis for OS, unfavorable karyotype, acute graft-versus-host disease (Gr III-IV), and delayed CR1 were still independent poor prognostic factors.

**Conclusion:** Our data suggested that delayed CR1 predicted a higher relapse rate and poorer post-transplant survival. Further large-scale studies are warranted to validate these findings.

**Keywords** Acute myeloid leukemia, Delayed CR1, Hematopoietic stem cell transplantation, Prognosis

## ADVERSE EFFECT OF MEASURABLE RESIDUAL DISEASE BY NGS CAN BE ABROGATED BY ALLOGRAFT IN AML PATIENTS WITH NORMAL KARYOTYPE

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**Purpose or Background:** Contemporary practice in acute myeloid leukemia (AML) does not consider the depth of remission following induction chemotherapy when choosing the type of consolidation therapy.

**Method or Case:** We evaluated treatment outcomes according to the measurable residual disease (MRD) status (defined as  $\geq 0.2\%$  mutation burden with next-generation sequencing; NGS) and the type of consolidation therapy in normal karyotype (NK)-AML patients.

**Results or Progress:** By sequencing 278 paired samples collected at diagnosis and first complete remission (CR1), we identified 357 mutations in 124 patients at diagnosis and tracked them at CR1. After excluding mutations associated with age-related clonal hematopoiesis (i.e., mutations in DNMT3A, TET2, and ASXL1 genes), we found that 79 mutations in 50/124 patients (40.3%) were persistent at CR1. A survival benefit over chemotherapy alone was observed with allogeneic stem cell transplantation (allo-SCT) in MRD-positive patients, but not in the MRD-negative group. Multivariate analyses in the MRD-positive subgroup confirmed that allo-SCT reduced the risk of relapse (HR;0.18, p=0.003), and improved overall (HR;0.26, p=0.004) and relapse-free survival (HR;0.24, p=0.001).

**Conclusion or Discussion:** The current study suggests that allo-SCT can be used to overcome the high relapse risk associated with MRD positivity, and the NGS-based MRD status at CR1 can help guide the selection of consolidation therapy in NK-AML.

**Keywords:** Normal karyotype, Acute myeloid leukemia, Minimal residual disease, Allogeneic stem cell transplantation, Prognosis

## INDUCTION AND MAINTENANCE THERAPY WITH VENETOCLAX IN RECURRENT PATIENTS OF ACUTE MYELOID LEUKEMIA AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

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**Purpose or Background:** To observe the efficacy of venetoclax regimen in recurrent patients of AML after allo-HSCT.

**Method or Case:** 7 patients of recurrent acute myeloid leukemia after allo-HSCT were collected from March 2018 to March 2019. The clinical efficacy was observed by therapy with Venetoclax.

**Results or Progress:** 6 of the 7 patients received at least one course of chemotherapy before using Venetoclax, and four received DLI, all of which were ineffective. After induction therapy with Venetoclax combined with low-dose cytarabine/cytarabine, 5 patients had complete remission (CR/CRi), 2 patients had no remission (NR), and the CR/CRi rate was 71.4%. The median total dose of Venetoclax in CR/CRi group was 9300 mg (7400 mg, 11000 mg), with a median application day. The median daily dose was 371.43 mg (264.29 mg, 523.8 mg) and the median remission time was 33 days (24, 42). In CR/CRi group, the duration of median neutrophil deficiency was 12 days (7,22), while that in NR group was 29 days (14,44), which was significantly longer than that in CR/CRi group. The complications were in proper order infectious fever in duration of neutrophil deficiency (4/7), herpes zoster (2/7 cases), sepsis (1/7) and tumor lysis syndrome (1/7). In CRI group, 1 patient was re-transplanted after remission, 3 patients were maintained with Venetoclax regimen, and 1 patient relapsed during maintenance therapy with Venetoclax alone. The median follow-up time was 140 days (120,354). In addition to the death of one patient who relapsed after remission, 6 patients survived with overall survival rate of 85.7%. The overall disease-free survival rate was 4/7 (57.1%). Two patients in NR group survived with disease (leukemia unremitted).

**Conclusion or Discussion:** The therapeutic effect of relapsed patients after allo-HSCT for AML is very poor. The Venetoclax-containing regimen has a certain curative effect and can become a new strategy for treatment choice.

**Keywords:** Acute myeloid leukemia, Allogeneic hematopoietic stem cell transplantation, Recurrence, Venetoclax

OP-023

## ANALYSIS OF GENETIC VARIANTS RELATED TO THE FIRST DAY AREA UNDER THE CURVE OF BUSULFAN IN PEDIATRIC PATIENTS RECEIVING HSCT WITH TARGETED DOSE BUSULFAN BASED CONDITIONING

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**Background:** Intensive monitoring and dose adjustment following therapeutic drug monitoring (TDM) of busulfan has improved outcomes after hematopoietic stem cell transplantation. However, personalized busulfan dosing using TDM is possible after administering the initial dose of busulfan. In this study, we identified genetic variants related to the first day area under the curve (AUC) of busulfan.

**Methods:** Targeted once-daily for four days intravenous busulfan with pharmacokinetic modeling was performed. The first dose of busulfan was 120 mg/m<sup>2</sup> for patients aged  $\geq 1$  year and 80 mg/m<sup>2</sup> for patients aged  $< 1$  year. Whole patients were divided into 119 discovery and 60 validation cohorts according to the whole exome sequencing order consecutively. Genetic biomarkers were selected by regression model with clinical covariate. Final model for classifying the first day AUC over 27,500 was trained in the discovery cohort using common variants through the elastic-net, and validated in the other cohort.

**Results:** Isoenzymes of Glutathione S-transferase (GST), GSTA2, GSTA3, and GSTA5, which are known to affect busulfan metabolism, were significant variants for the first day AUC. The additive model of GSTA5 variant was significant with a p-value  $< 0.001$  for both discovery and validation, and the coefficients were -3218.24 and -4720.54, respectively. Aralkylamine N-acetyltransferase (AANAT) and Acyl-CoA synthetase (ACSL5) are significant for the first day AUC in both discovery and validation cohorts. The area under the receiver operating characteristic of the prediction model was 0.948 on discovery and 0.797 on validation cohorts.

**Conclusion:** Several genetic biomarkers that affect the first day AUC were identified, and the trained models using variants highly predicted the patients with high first day AUC. Further analysis is needed on the effects of the genetic biomarkers on toxicities and treatment outcomes. Further validation and replication studies in a larger group of patients are needed.

**Keywords :** Busulfan, Variants, Pharmacogenomic, stem cell transplantation



## ALLOGENEIC HEMATOPOIETIC STEM CELL TRANPLANTATION UNDER 2 YEARS OF AGE: A SINGLE-CENTER EXPERIENCE

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**Purpose:** To analyze outcomes of allogeneic hematopoietic cell transplantation (HSCT) in children under 2 years of age.

**Method:** We retrospectively analyzed the medical records of 83 patients who received an allogeneic HSCT under 2 years of age at Asan Medical Center Children's Hospital between January 2001 and December 2018.

**Results:** Of the total patients with a median age of 14 months (range, 3-24months) received an allogeneic HSCT under 2 years of age. The median follow-up time from transplantation day was 56 months ranged from 6 days to 170 months. 52 patients (65%) had a malignant diagnosis including acute lymphoblastic leukemia (20, 38.5%), acute myeloblastic leukemia (17, 32.7%), mixed phenotype acute leukemia (2, 3.8%), myelodysplastic syndrome (2, 3.8%), and other leukemia (11, 21.2%). 31 patients (37.3%) had non-malignant disease including aplastic anemia (7, 22.6%), metabolic disease (3, 9.7%), primary immune deficiency (9, 29%), hemophagocytic lymphohistiocytosis (9, 29%), and other diseases (3, 9.7%). The 5-year overall survival (OS) rate of total patients was 69.9%. The OS rate of patients with malignant disease and non-malignant disease were 63.5%, and 80.6%, respectively. The OS rate of patients who underwent reduced intensity conditioning regimen was significantly better than myeloablative conditioning regimen (81.4% vs 57.5%,  $p = 0.021$ ). Of the patients with malignant diseases, 11 patients died from transplant-related toxicity, 5 patients relapsed and 1 died of other cause. Among non-malignant disease, 5 patients died from transplant-related toxicity. Seven patients received a 2nd HSCT, 6 patients owing to relapse and 1 patient for graft failure. The OS rate of patients who underwent transplantation using matched sibling (83.3%) was better than using unrelated donor (65.4%) or haploidentical donor (73.7%).

**Conclusion:** Allogeneic HSCT for infant and toddlers has poorer outcome than other ages. An approach to reduce transplatation associated mortality should be established.

**Keywords:** Hematopoietic stem cell transplantation, infant

OP-025

## IMPACT OF HLA CLASS I ALLELE MISMATCH ON VIRAL INFECTION WITHIN 100 DAYS AFTER CBT

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**Background:** Viral infections often occur within 100 days of cord blood transplantation (CBT). We studied the impact of human leukocyte antigen (HLA) class I incompatibility between donor and recipient on viral infection incidence within 100 days of CBT.

**Method:** We retrospectively analyzed 121 patients undergoing 126 CBTs (excluding primary graft failure) in Kyoto University Hospital from February 2003 to January 2019. Viral infections were defined as infections of patients' somatic cells by viruses detected via pathology or molecular biology. Cytomegalovirus (CMV) antigenemia was distinguished from viral infections, because in such cases, the infected cells are donor-derived cells.

**Results:** HLA-C and HLA-A mismatches in graft-versus-host disease (GVHD) direction were associated with a significantly high viral infection incidence (HLA-A: 42.7% vs. 25.8%, HR 1.86,  $P=0.049$ ; HLA-C: 43.9% vs. 17.6%, HR 2.94,  $P=0.015$ ). More than 2/6 HLA class I allele mismatches in GVHD direction were associated with a significantly high viral infection incidence (50.0% vs. 26.9%, HR 2.29,  $P=0.010$ ). HLA class I incompatibility was not associated with steroid use for GVHD, engraftment syndrome, or pre-engraftment immune reaction (70.4% vs. 64.2%,  $P=0.53$ ) or with CMV antigenemia within 100 days of CBT (65.8% vs. 70.1%,  $P=0.82$ ). HLA-DR mismatch in GVHD direction was not associated with viral infection incidence (34.1% vs. 32.6%, HR 1.13,  $P=0.72$ ).

**Conclusion:** Considering HLA class I allele compatibility, including HLA-C compatibility, is important while selecting CBT donors.

**Keywords:** HLA, viral infection, cord blood transplantation

## FAVORABLE OUTCOME OF POST-TRANSPLANTATION CYCLOPHOSPHAMIDE HAPLOIDENTICAL PERIPHERAL BLOOD STEM CELL TRANSPLANTATION WITH TARGETED BUSULFAN-BASED MYELOABLATIVE CONDITIONING IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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**Purpose or Background:** Haploidentical hematopoietic stem cell transplantation (haplo-HSCT) is an effective method for various malignant hematologic diseases, particularly in cases when an HLA-matched donor is not available. But, there are not sufficient data for haplo-HSCT in pediatric acute lymphoblastic leukemia (ALL) and National Health Insurance did not cover it. To prove the effectiveness and safety, outcome of haplo-HSCT in pediatric hLL was analyzed.

**Method or Case:** We retrospectively reviewed the medical chart of 16 pediatric patients (median age 9.3 years, range 0.9-14.3) who was diagnosed as ALL and underwent haplo-HSCT using a targeted busulfan-based myeloablative conditioning regimen and post-transplantation cyclophosphamide (PTCy) at Seoul National University Children's Hospital from 2005 to 2018.

**Results or Progress:** Twelve patients underwent haplo-HSCT in first complete remission (CR) because of poor prognosis factors (5 induction failure, 4 initial WBC >200,000/ $\mu$ L, 2 BCR/ABL positive, 1 infant ALL, and 1 hypodiploidy). Four patients (25%) were in second CR. There was no engraftment failure. The cumulative incidence rates of grade II to IV, grade III to IV acute graft-versus-host disease (GVHD) and extensive chronic GVHD were 46.7%, 0%, and 13.3% respectively. The relapse incidence rate was 25% and treatment-related mortality was 0%. The event-free survival rates and overall survival were 75% and 81.3%, respectively.

**Conclusion or Discussion:** Haplo-HSCT using a targeted busulfan-based myeloablative conditioning, peripheral blood stem cell and PTCy was an effective and feasible treatment for pediatric ALL patients.

**Keywords:** Post-Transplantation Cyclophosphamide, Haploidentical Peripheral Blood Stem Cell Transplantation, Targeted Busulfan-Based Myeloablative Conditioning, Acute Lymphoblastic Leukemia

OP-027

## THE ROLE OF DONOR LYMPHOCYTE INFUSION (DLI) FOR MIX CHIMERISM TREATMENT IN SCID INFANTS

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**Purpose or Background:** Allogenic hematopoietic stem cell transplantation (HSCT) is the only curative treatment available for severe combined immunodeficiency (SCID); however, mix chimerism remain one of the major concerns post transplantation. Although donor lymphocyte infusion (DLI) has been used to prevent relapse in a variety of malignant diseases, the utility of this modality in nonmalignant disorders such as SCID is limited. As such, in this study we sought out to explore the efficacy and outcomes of DLI after allogenic HSCT in pediatric patients with SCID during 2008 and 2018.

**Method or Case:** This is a retrospective study on all SCID patients with history of mix chimerism who underwent DLI. All patients received escalating dose of CD3+ from  $1 \times 10^7$  cell/kg to  $5 \times 10^7$  cell/kg every 3 to 4 weeks. The Chimerism was checked 2 weeks after every DLI. If acute Graft versus Host Disease (GvHD) was developed or full chimerism was achieved DLI was stopped.

**Results:** Overall 8 patients including five males and three females with median age 6 months (range, 1.5-12) were studied for this investigation. At the final assessment of the DLI efficacy and safety, one patient (12.5%) experienced full donor chimerism ( $>95\%$ ), six (75%) experienced a stable mix chimerism while one patient (12.5%) showed no-response. Two patients (25%) developed acute GvHD grade IV and one patient (12.5%) developed extensive chronic GvHD. At a median 28.4 (range, 3-65) months after DLI, seven patients were alive (87.5%), while one infant (12.5%) who received unrelated mismatched donor expired due to disseminated invasive tuberculosis.

**Conclusion or Discussion:** The results show the effectiveness of DLI as a safe intervention for SCID children which developed a mix chimerism after HSCT. Due to the small sample size, it needs a conducted well designed multi-center study to analysis the role of GvHD and other variables in the DLI outcomes.

**Keywords:** Severe combined immunodeficiency, Donor lymphocyte infusion, Infant, Allogenic hematopoietic stem cell transplantation

## NONINFECTIOUS LUNG COMPLICATIONS AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN: A SINGLE CENTER EXPERIENCE

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**Purpose or Background:** Late-onset noninfectious pulmonary complications (LONIPCs) includes bronchiolitis obliterans syndrome (BOS), interstitial lung disease, thoracic air leak syndrome, pulmonary vascular diseases and pleural effusion which occur beyond three months following allogeneic hematopoietic stem cell transplantation (HSCT). Incidence of LONIPCs ranges from 10 to 26% in previous reports, however well-analyzed studies among children are rare.

**Method or Case:** In this study we retrospectively reviewed the pediatric patients who received allogeneic HSCT in Severance hospital from 1st January 2005 to 31st December, 2018. All medical charts and imaging studies of the patients were reviewed by a pediatric transplant specialist, three radiologists, and one experienced pulmonary physician.

**Results or Progress:** During 13 years, 251 HSCTs were performed for 241 patients. Among them, chest CT scans to check pulmonary complication were taken in 123 cases (49.0%), in 118 patients (48.9%) after transplantation. Leukemia (72.9%), aplastic anemia (8.4%) were the most common diseases of the patients. Through image review, LONIPCs were found in 46 cases (18.7%) of transplantation in 46 patients (19.1%). These are similar incidence rates compared with adults. BOS was most common complication among LONIPCs, diagnosed in 40 patients (87.0%), BOOP was found in 7 cases (15.2%), a few had thoracic air leak syndrome together. For median follow up duration of 28.9 months, overall survival of all HSCT patients was 58.7%. Although there were no meaningful survival difference in groups with or without LONIPCs, patients with LONIPCs showed higher early mortality rate.

**Conclusion or Discussion:** As pulmonary complications can lead to dismal outcomes of HSCT, we are going to expand our study to find risk factors of LONIPCs. Close monitoring, and early identification of LONIPCs and prophylactic treatment is very important.

**Keywords:** allogeneic hematopoietic stem cell transplantation, pulmonary complication, bronchiolitis obliterans, organizing pneumonia, graft versus host disease

## A PHASE 3 TRIAL OF THYMOGLOBULINE FOR PREVENTION OF CHRONIC GVHD IN TRANSPLANTATION FROM AN HLA-MATCHED SIBLING: AN INTERIM REPORT

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**Background:** Antihuman T-lymphocyte immune globulin (ATG) has been shown to lower the incidence of chronic graft-versus-host disease (cGVHD) after allogeneic hematopoietic stem cell transplantation (allo-HSCT) from an unrelated donor. However, there are few studies to show the role of ATG in allo-HSCT from matched sibling except a recent randomized trial of ATG-Fresenius (NEJM 2016).

**Method:** We have been conducting a prospective, single center, open-label, randomized trial of ATG-Thymoglobulin as a part of the conditioning regimen. The primary endpoint was the cumulative incidence (CI) of cGVHD at 2-year evaluation. A total of 120 patients with acute leukemia were planned to be enrolled and assigned randomly in a 1:1 ratio to receive or not receive ATG-Thymoglobulin (1.25 mg/kg on 3 and two days before allo-HSCT) stratified according to the refined Disease Risk Index and conditioning intensity.

**Results:** This interim report includes 67 patients at least six months of follow-up period after allo-HSCT. After a median 420 days of follow-up (range 180 – 850), the CI of cGVHD in ATG group (n=33) and non-ATG group (n=34) was 28.3% and 71.3% (p=0.003), respectively. The CI of moderate to severe cGVHD was 9.3% in the ATG group and 44.5% in the non-ATG group (p=0.003). The rate of disease-free and overall survival was similar in the ATG group and the non-ATG group. There were no significant between-group differences in the CI of relapse, infectious complications, acute GVHD, or other allo-HSCT-related adverse events.

**Discussion:** The inclusion of ATG-Thymoglobulin even with a relatively lower dose compared with a recent recommendation (7.5 mg/kg) by EBMT/ELN resulted in a significantly lower rate of cGVHD after allo-HSCT in this interim analysis. The completion of this study will reveal the role of ATG-Thymoglobulin for prevention of cGVHD in allo-HSCT from an HLA-matched sibling, which would be the first phase 3 trial with Thymoglobulin to our knowledge.

**Keywords:** Thymoglobulin, chronic GVHD, allo-HSCT, matched sibling

## HAPLOIDENTICAL BONE MARROW TRANSPLANTATION FOR PATIENTS WITH SEVERE APLASTIC ANEMIA-II DEGENERATED FROM NON-SEVERE ACQUIRED APLASTIC ANEMIA

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**Purpose:** To investigate the efficacy of haploidentical bone marrow transplantation (haplo-BMT) for severe aplastic anemia II (SAA-II) degenerated from non-severe aplastic anemia (NSAA).

**Patients and methods:** 22 SAA-II patients were recruited and underwent haplo-BMT from February 2015 through May 2018. Treatment protocol and written informed consent forms were well prepared. FLU-BU/CY-ATG served as conditioning regimen. G-CSF-primed stem cells  $\geq 3 \times 10^6/\text{kg}$  were infused. Tacrolimus, mycophenolate mofetil and methotrexate as prophylaxis for aGVHD.

**Results:** 20 of 22 patients successfully engrafted with OS of  $90.9 \pm 3.8\%$  at a follow-up of 36 months. Noteworthy, one patient had secondary graft failure, and then a successful second haplo-BMT, one died of severe infection in conditioning regimen, and one died of fungal lung infection 15 months post BMT. 11 of 21 patients suffered with aGVHD, 8 recipients with grade I-II aGVHD, 3 with grade III-IV aGVHD. 7 of 21 experienced limited cGVHD. During BMT, 12 patients experienced infections. 9 had EBV reactivation Post-BMT, among them, one was diagnosed PTLD, and one with probable EBV disease, the two recipients recovered with infusion of rituximab. Peripheral blood examination well recovered and bone marrow cellularity from 8 patients rose up to 30%-60% one year post BMT.

**Conclusion and Discussion:** SAA-II usually developed from NSAA, it has characteristics of a longer disease duration, a worsened quality of life, and no efficacious treatments. Therefore, haplo-BMT should be an option without an HLA-matched donor. FLU-BU/CY+ATG regimen has a successful engraftment in all 21 survived patients, indicating an effective conditioning regimen for SAA-II. Haplo-BMT achieved a 3-year OS of  $90.9 \pm 3.8\%$  in 22 SAA-II patients, indicating an effective therapy, and undoubtedly an option of salvage therapy for SAA-II patients. The promising outcomes shed light on the treatment strategy of SAA-II, when no HLA-sibling donor, or no efficacious ways to improve the status of SAA-II.

**Keywords:** severe aplastic anemia II, haploidentical bone marrow transplantation, efficacy, non-severe aplastic anemia

OP-031

## MATCHED FAMILY VERSUS ALTERNATIVE DONOR HEMATOPOIETIC STEM CELL TRANSPLANTATION IN THALASSEMIA MAJOR: EXPERIENCE OVER 10 YEARS FROM A TERTIARY REFERRAL CENTER IN SOUTH INDIA

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**Introduction:** With increasing accessibility to alternate donors, there have been significant advances in achieving cure for thalassemia major with hematopoietic stem cell transplantation (HSCT). We aimed to analyse the impact of family and alternate donor HSCT on morbidity and mortality post HSCT.

**Methods:** We conducted a retrospective study in the department between July 2007 and December 2018. Children diagnosed to have Thalassemia major and who underwent HSCT were included.

**Results:** A total of 264 children were included with a median age of 6 years (M: F – 1.4:1). The graft source was matched family donor (MFD) 76% (parent 15%, sibling 85%), matched unrelated donor 22%. All children received myeloablative conditioning regimen (Busulfan based in 7%, Treosulfan based 93%). Peripheral blood stem cells were used in 63%, bone marrow 36%, umbilical cord blood unit 1%. During the peri-engraftment period, bacterial sepsis was noted equally in both the groups (25%), while there was a higher incidence of PRES in the MUD group (10% vs 3%). Although engraftment was achieved in 97% transplants across both the groups, there was higher trend towards mixed chimerism among the MFD group (12% vs 2%) and whole blood donor lymphocyte infusions were used to achieve 100% chimerism in them. Acute graft versus host disease (GvHD) was noted in a significant higher proportion of children in the MUD group (60% vs 21%) with 42% children in the MUD group requiring treatment for chronic GvHD, as was the case with immune cytopenia (MUD 17% vs MFD 2%). Viral reactivation was higher among those receiving MUD HSCT (27% vs 2%). Overall survival in our cohort was 93% and disease free survival of 89.4% with a median follow up of 96 months (MFD 95%, MUD 87%).

**Conclusion:** Alternative donor transplants for thalassaemia major offer an overall survival of 90%. However, the morbidity and the post transplant events are higher in MUD. Meticulous follow up of graft kinetics, viral reactivation and tackling GvHD effectively and CD34 limit of  $5 \times 10^6$ /kg helps to improve the outcome.

**Keywords :** Thalassemia, HSCT, Matched unrelated donor HSCT, Outcome



## DISEASE RISK COMORBIDITY INDEX FOR PATIENTS RECEIVING HAPLOIDENTICAL ALLOGENEIC HEMATOPOIETIC TRANSPLANTATION

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**Purpose or Background:** We aimed to develop a disease risk comorbidity index (DRCI) based on Disease Risk Index (DRI) and Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) in patients receiving haploidentical hematopoietic stem cell transplantation (haplo-HSCT).

**Method or Case:** We examined 889 patients undergoing haplo-HSCT from 2015 to 2016. We used a Cox multivariable model to identify factors prognostic of disease-free survival (DFS) in a training subset (n = 593). A weighted score using these factors was assigned to the remaining patients (validation cohort; n = 296). This work was supported by the Capital's Funds for Health Improvement and Research (grant number 2018-4-4089).

**Results or Progress:** The multivariable model identified two independent predictors of DFS: DRI and HCT-CI before HSCT. A weighted score of 2 was assigned to very high risk DRI, and a weighted score of 1 was assigned to high-risk DRI and intermediate- and high-risk HCT-CI in the scoring system (i.e., haplo-HSCT). In the validation cohort, the 3-year DFS was 65.2% (95% CI, 58.2–72.2%), 55.8% (95% CI, 44.9–66.7%), and 32.0% (95% CI, 5.8–58.2%) for the low-, intermediate- and high-risk group, respectively (P=0.005). Haplo-DRCI can predict relapse (P<0.001), non-relapse mortality (NRM, P<0.001), DFS (P<0.001), and overall survival (OS, P<0.001) in total population and in disease-specific subgroups, particularly in acute leukemia patients. Increasing score was also significantly predictive of increased relapse (P<0.001), increased NRM (P=0.001), decreased DFS (P<0.001), and decreased OS (P<0.001) in an independent historical cohort (n=526).

**Conclusion or Discussion:** These data confirmed that haplo-DRCI can effectively risk stratifies haplo-HSCT recipients and provide the tool to better predict who will best benefit from haplo-HSCT.

**Keywords:** disease risk index, disease risk comorbidity index, hematopoietic cell transplantation comorbidity index, hematopoietic stem cell transplantation, haploidentical

OP-033

## POST-TRANSPLANTATION CYCLOPHOSPHAMIDE FOR GRAFT-VERSUS-HOST DISEASES PREVENTION IN HIGHER-RISK MYELODYSPLASTIC SYNDROME

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**Purpose or Background:** Allogeneic hematopoietic cell transplantation (HCT) is considered an only curative treatment for myelodysplastic syndrome (MDS). However, mortality rates after allogeneic HCT in MDS patients are high, which is attributable to disease relapse and transplantation-related complications including graft-versus-host diseases (GVHD). In this pilot study, we aimed to evaluate the feasibility and efficacy of post-transplantation cyclophosphamide (PTCy) for GVHD prophylaxis in higher-risk MDS patients.

**Method or Case:** Patients with higher-risk MDS defined by international prognostic scoring system > 1.0 or bone marrow blasts > 5% during the course of MDS before HCT were eligible for the study. Patients received busulfan-based conditioning regimens (age ≤55 years, 3.2 mg/kg × 4 days; age >55 years, 3.2 mg/kg × 2 days). GVHD prophylaxis consists of 50 mg/kg/day of PTCy on 3 and 4 days and cyclosporine/mycophenolate mofetil from 5 days after G-CSF-mobilized peripheral blood stem cell graft infusion.

**Results or Progress:** Between August 2017 and January 2019, twenty-five patients were enrolled. The median age at HCT was 53 years (range, 25–69) and more male patients were included. At the time of HCT, 12 patients (48.0%) were in complete remission (CR) or marrow CR. After 2-days (n=15) or 4-days (n=10) of busulfan-containing conditioning, patients received peripheral blood allografts from matched sibling (n=7), matched unrelated (n=9) or haploidentical familial donors (n=9). Patients achieved neutrophil and platelet engraftment after median 15 and 29 days with cumulative incidence of 92.0% and 76.0%, respectively. The incidences of grade II-IV and III-IV acute GVHD and chronic GVHD were 17.7%, 10.0%, and 36.0%, respectively. After a median follow-up of 11.3 months, the estimated 1-year overall survival, event-free survival, relapse and non-relapse mortality incidences were 65.5%, 51.7%, 15.3%, and 31.3%, respectively.

**Conclusion or Discussion:** PTCy was effective as GVHD prophylaxis after allogeneic peripheral blood cell transplantation for high-risk MDS patients.

**Keywords:** Post-transplantation cyclophosphamide, Myelodysplastic syndrome, Higher-risk, Busulfan

## HEMATOPOIETIC RECOVERY AND TRANSFUSION NEED AFTER HAPLOIDENTICAL TRANSPLANTATION IN BETA THALASSEMIA PATIENTS

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**Purpose:** At present, thalassemia free survival after matched-related and unrelated donor transplant is about 80-90%. Despite bone marrow donor registries and cord blood banks, 20-25% of the patients still do not find a suitable matched donor. Haploidentical stem cell transplant (HISCT) is an alternative transplant option for these patients. We aimed to determine the outcome of HISCT in thalassemic patients.

**Method:** Between 2014-2018, 16 thalassemic patients underwent HISCT. The median age of patients was 5 (1-8) years with male preponderance (n=10, 62.5%). Stem cell source was bone marrow in 5 (31%) while peripheral blood in 11 (69%) of patients. Mean stem cell dose was  $5.6 \pm 2.9 \times 10^6$  cells/kg. Standard preparative regimen and graft versus host disease (GvHD) prophylaxis were given. Patients were observed for hematopoietic recovery and transplant-related mortality including acute and chronic GvHD, primary and secondary graft failure and infectious complications.

**Results:** Nine (56.25%) of sixteen patients were engrafted with full donor chimerism. Twelve (75%) patients belonged to Pesaro class I and 4 (25%) to Class II patients. Median time to neutrophil and platelet engraftment were 13(11-20) and 16 (12-36) days respectively. Primary and secondary graft failure was observed in 3 (19%) and 4 (25%) patients respectively. Acute GvHD of gut and skin (grade II-III) was observed in 2 patients each, within the first 100 days post-transplant. Cytomegalovirus reactivation occurred in 50% of patients. Invasive fungal infection was not observed in any of the patients. Culture proven bacterial infection was documented in 62% of patients requiring intravenous antibiotics. Overall and relapse-free survivals were 81.25 % and 56.25% respectively over a median follow-up of 500 (21-1,757) days.

**Conclusion:** In view of our results, haploidentical transplant is a suitable modality for thalassemic patients lacking a full-matched donor in Pakistan.

**Keywords:** Beta Thalassemia Major, Haploidentical BMT, Hematopoietic recovery

OP-035

## IMMUNOLOGICAL BIOMARKER PROFILE ASSOCIATED WITH CLINICAL OUTCOMES OF STEROID-REFRACTORY CHRONIC GVHD PATIENTS TREATED WITH MULTIPLE MSC INFUSIONS IN A PHASE I CLINICAL TRIAL

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**Background:** Chronic graft-versus-host disease (cGVHD) is a long-term complication of allogeneic hematopoietic stem cell transplantation associated with poor quality of life and increased morbidity and mortality. Currently, there is no standardized treatment available for patients who do not respond to steroids. As an alternative to immunosuppressants, mesenchymal stem cells (MSCs) have been suggested to treat steroid-refractory GVHD.

**Method:** To evaluate the safety and efficacy of repeated infusions of MSCs, we treated ten severe steroid-refractory cGVHD patients intravenously with MSCs produced from third-party bone marrow donors biweekly for a total of four doses. Each dose contained  $1 \times 10^6$  cells/kg body weight from the same donor and same passage.

**Results:** Ten patients with various organ involvement were enrolled. All ten patients received their planned four doses of MSCs, administering a total of 40 infusions during the study. MSCs were well tolerated with no immediate or delayed toxicities. After 8 weeks of the first MSC infusion, all ten patients showed partial response showing alleviation in clinical symptoms and increased quality of life. Two patients died due to relapse from primary disease. Immunological analyses revealed reduction in inflammatory markers including ST2, CXCL10, and osteopontin following MSC treatment.

**Conclusion:** Repeated infusions of MSCs was feasible and safe and may be an effective salvage therapy in patients with steroid-refractory cGVHD. Further large-scale clinical studies with long-term follow up is needed in the future to determine the role of MSCs in cGVHD.

**Keywords:** Mesenchymal stem cells, chronic graft-versus host disease, cell therapy, clinical trial, allogeneic hematopoietic stem cell transplantation, immunological analysis

## HAPLOINSUFFICIENCY OF NR3C1 DRIVES GLUCOCORTICOID RESISTANCE IN ADULT ACUTE LYMPHOBLASTIC LEUKEMIA CELLS BY DOWN-REGULATING THE MITOCHONDRIAL APOPTOSIS AXIS, AND IS REVERSIBLE BY BCL-2 BLOCKAGE

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**Purpose or Background:** Relapse represents the leading cause of death in both child and adult patients with acute lymphoblastic leukemia (ALL). Development of chemo-resistance is ultimately responsible for treatment failure and relapse, therefore understanding the molecular basis underlying resistance is imperative for developing innovative treatment strategies. Glucocorticoids (GCs) such as dexamethasone and prednisolone are the backbone of combination chemotherapy regimens for treating all lymphoid tumors. However, the biological mechanisms of primary GC resistance in ALL is not completely understood. We previously performed a longitudinal whole-exome sequencing analysis on diagnosis/relapse pairs from adult patients with ALL. Our data revealed that relapse-specific truncation mutations in the NR3C1 gene, encoding the GC receptor, are frequently detected.

**Method or Case:** In the current study, we used discovery-based strategies including RNA sequencing (RNA-seq) and CRISPR/Cas9, followed by confirmatory testing, in human ALL cell lines, bone marrow blast samples from ALL patients and xenograft models, to elucidate the mechanisms responsible for resistance.

**Results or Progress:** Our results revealed a positive correlation between endogenous expression of NR3C1 in ALL cells and sensitivity to GCs and clinical outcomes. We further confirmed that ectopic expression of NR3C1 in ALL cells could reverse GC resistance, while deletion of NR3C1 confers resistance to GCs in ALL cell lines and xenograft models. RNA-seq analysis revealed a remarkable abundance of gene signatures involved in pathways in cancer, DNA replication, mismatch repair, P53 signalling, cell cycle, and apoptosis regulated by NR3C1. Significantly increased expression of pro-apoptotic genes including BCL2L1/Bim, BMF, BAD, BAX and BOK, and decreased transcription of anti-apoptotic genes including BCL2, BCL2L1 and BAG2 were observed in GC-resistant ALL cells following ectopic expression of NR3C1. Finally, we explored that GC resistance in ALL cells with haploinsufficiency of NR3C1 can be reversible by Bcl-2 blockage.

**Conclusion or Discussion:** Our findings suggest that the status of NR3C1 gene mutations and basal expression levels of NR3C1 in ALL cells are associated with sensitivity to GCs and clinical treatment outcomes. Early

intervention strategies by rational combination of Bcl-2 blockage and GCs may constitute a promising new treatment option to reversing GC resistance and significantly improving the chances of treating poor prednisone responders.

**Keywords:** Haploinsufficiency, NR3C1, Glucocorticoid resistance, Acute lymphoblastic leukaemia, Mitochondrial apoptosis axis, Bcl-2 blockage

## IFN- $\gamma$ , AND POLY(I:C) PRIMED MSCs ENHANCE THE THERAPEUTIC EFFECTS ON DSS INDUCED COLITIS VIA ENHANCING INDOLEAMINE 2, 3-DIOXYGENASE WITH INDUCTION OF REGULATORY T CELLS

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Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine caused by chronic and excessive inflammation. We previously demonstrated that mesenchymal stem cells (MSCs) treated with poly(I:C), a TLR3 ligand, more profoundly induced IDO, which is a therapeutically relevant immunosuppressive factor (Immune Netw. 2016;16(6):358-365). The goal of the study was to determine how poly(I:C) can enhance the therapeutic efficacy of bone marrow-derived MSCs for the treatment of IBD. To compare the therapeutic effects between naïve MSCs and primed MSCs on murine colitis, mice (C57BL6) were administered with 2.5% dextran sodium sulfate (DSS) in drinking water for 5 days and injected with MSCs intraperitoneally on days 1 and 3 following DSS ingestion. The disease activity index score and body weight loss were significantly improved after injection of the primed MSCs. Also the pathological severity of the colon was significantly better in primed MSCs treated group. In primed MSCs treated group, the frequency of T cells in spleen and mesenteric lymph node was markedly decreased and foxp3 expressing regulatory T cells were more expanded. Expression of proinflammatory cytokines such as IL-1 $\beta$ , TNF $\alpha$  and IL-6 mRNA was profoundly reduced, whereas that of COX-2, PTGES3 and IDO mRNA was significantly increased in colon tissues of mice treated with primed MSCs. To determine the effect of the primed MSCs on the differentiation of regulatory T cells, we co-cultured with T cells with or without primed MSCs. Compared with the naïve MSCs, the primed MSCs significantly increased the regulatory T cell generation. This was restored by treatment with IDO inhibitor, D-1MT and L-1MT. In conclusion, we demonstrate that primed MSCs with poly(I:C) improve their efficacy in treating DSS-induced colitis, and this effect at least partly depends on the enhancement of their immunosuppressive activity through increasing their production of IDO.

**Keywords:** Mesenchymal stem cells, Dextran sulfate sodium (DSS)-induced colitis, Toll-like receptors, Indoleamine 2,3-dioxygenase

OP-038

## IMMUNOSUPPRESSANTS FACILITATE EBV REACTIVATION BY INHIBITING V $\delta$ 2+ T CELLS ACTIVITIES AFTER HEMATOPOIETIC TRANSPLANTATION

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**Background:** Epstein-Barr virus (EBV) reactivation is a common threat after allogeneic HSCT. Previous studies suggest that ATG and CsA are associated with EBV reactivation, it's correlation with mycophenolate mofetil (MMF) remains unclear. Specific T-cell subsets involved in the immunosuppressants-related EBV reactivation await clarified. We previously demonstrated that V $\delta$ 2+ T cells inversely correlated to EBV reactivation after haploidentical HSCT (haploHSCT). Whether the impaired reconstitution and anti-EBV capacity of V $\delta$ 2 cells are attributed to immunosuppressants remains unknown.

**Methods:** Ex-vivo expansion and EBV-specific cytotoxicity of V $\delta$ 2 cells, with or without mycophenolic acid (MPA) and CsA treatments, were detected by flow cytometry. Immunodeficient NOD-Prkdcscid-Il2rgtm1/Vst (NPG) mice were used to evaluate the impacts of MMF and CsA on V $\delta$ 2-cell-anti-EBV-LCL capacity in vivo. Two clinical cohorts (n = 85 of each group) of haploHSCT recipients administrated different courses of MMF were included. Recoveries of T-cell subsets and incidences of EBV reactivation were compared.

**Results:** Proliferation and IFN- $\gamma$  expression of V $\delta$ 2 cells were induced after pamidronate stimulation, those were attenuated by MPA or CsA (P values all < 0.001). The cytotoxicity of V $\delta$ 2 cells on EBV-LCLs was impaired by MPA in cultured cells and mouse models (P = 0.035 and 0.036). In contrast, the negative influence of CsA tended to be subtle in this context (P = 0.080 and 0.059). Clinical study showed V $\delta$ 2-cell recoveries were continuously increased after reducing the course of MMF, accompanied with a decreased incidence of EBV reactivation (from 26% to 13%, P = 0.033). Day-30 V $\delta$ 2 level remained an independent factor for EBV reactivation in patients with different MMF durations.

**Discussion:** This study clarified a negative influence of common-used immunosuppressive drugs on EBV-cytotoxic V $\delta$ 2 cells. The findings suggest that appropriately relieving immunosuppression probably facilitates anti-EBV immunity through recovering V $\delta$ 2 cell function at early stage after allogeneic HSCT.

**Keywords:** immunosuppressant, Hematopoietic stem cell transplantation, Epstein-Barr virus (EBV), V $\delta$ 2 cells





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# Poster Presentation



PP-001

## COMPARISON OF AUTOLOGOUS VERSUS MATCHED SIBLING DONOR STEM CELL TRANSPLANTATION FOR PATIENTS WITH PHILADELPHIA CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA- ANALYSIS FROM A SINGLE CENTER OF CHINA

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**Purpose or Background:** In the era of tyrosine kinase inhibitors (TKIs), allogeneic hematopoietic stem cell transplantation (SCT) is still considered a standard treatment for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) achieving complete remission (CR). We retrospectively analyzed the outcomes of patients who received either auto-SCT or MSD-SCT to find out who were more eligible for auto-SCT in patients with Ph+ ALL.

**Method or Case:** We investigated the outcomes of 78 adult patients with PH+ ALL who received myeloablative SCT in our center from Jan 2008 to Dec 2017.

**Results or Progress:** The estimated relapse rates(RR) at 3 years were 45.7% after auto-SCT and 27.2% after MSD-SCT ( $P = 0.127$ ) and the non-relapse mortality(NRM) rate were 17.0% and 3.2% ( $P = 0.072$ ). The estimated leukemia-free survival(LFS) were 51.1% and 55.8% ( $P = 0.803$ ), while overall survival(OS) rates were 71.8% and 74.1% ( $P = 0.919$ ), respectively. By multivariate analysis, achievement of complete molecular response (CMR) within 3 months and sustaining CMR up to transplantation(s3CMR) was associated with lower risk of RR (hazard ratio [HR], 3.581,  $P = 0.004$ ) and higher LFS ([HR], 2.439,  $P = 0.015$ ). In auto-SCT group, patients with s3CMR demonstrated significantly higher OS (84.0% vs. 40.0%,  $P = 0.029$ ), higher LFS (70.3% vs. 20.0%,  $P = 0.020$ ) and lower relapse rate (RR)( 24.9% vs. 80.0 %,  $P = 0.008$ ) as compared to non-s3CMR patients. In MSD-SCT group, the s3CMR only correlated with lower RR(14.4 % vs. 39.6%,  $P = 0.039$ ) and the OS/LFS was similar between s3CMR patients and non-s3CMR patients.

**Conclusion or Discussion:** Auto-SCT with maintenance therapy after SCT appears to be an attractive treatment option for patients with Ph+ ALL especially for those s3CMR was kept up to transplantation. For non-s3CMR patients, allogeneic transplantation may be more effective due to lower relapse.

**Keywords:** autologous, matched sibling donor, stem cell transplantation, Philadelphia chromosome-positive, acute lymphoblastic leukemia, sustaining complete molecular response

## EVALUATION OF TAX, HBZ AND BCL-XL GENE EXPRESSION IN ADULT T CELL LEUKEMIA/LYMPHOMA (ATL) AND HEALTHY CARRIERS.

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**Purpose or Background:** HTLV-I is a worldwide distribution retrovirus with 10-20 million infected individuals. North east of Iran especially Mashhad is one of the endemic areas. In spite of the healthy carriers are the majority of HTLV-I-infected individuals but small proportion of infected population developed two progressive diseases: ATL and HAM/TSP. ATLL is an Adult T Cell leukaemia lymphoma caused by the aggressive T-cell proliferation that infected by HTLV-1 and is associated with a very poor prognosis. BCL-XL belongs to BCL2 family which inhibits apoptosis in cell so over express of this gene may promote the uncontrolled cell proliferation. TAX as an oncoprotein is the main cause of malignancy which may interrupt in apoptosis, therefore in this study co expression of TAX and BCL-XL were evaluated.

**Method or Case:** In this study, 37 HTLV-I infected individuals including 17 asymptomatic and 20 ATL subjects were investigated. mRNA were extracted and convert to cDNA from Peripheral blood mononuclear cells (PBMCs) then expression of TAX and BCL-XL investigated by TaqMan qPCR.

**Results or Progress:** The analysis of data showed a significant difference in mean of TAX expression among study groups (ATL and carriers  $P = (0.003)$ ). There is no statically difference between the BCL-XL gene expression ( $p = 0.32$ )

**Conclusion or Discussion:** The present study demonstrated that TAX gene expression was higher in ATL group in comparison with healthy carriers and there is no difference for BCL-XL. Therefore, anti apoptotic pathway may not strongly involved into ATLL oncogenesis during HTLV-I infected subjects and TAX may is a prognostic factor for development of HTLV-I associated diseases and can be used as a monitoring marker for the efficiency of therapeutic regime and prognosis.

**Keywords:** ATLL, HTLV-1, BCL-XL

PP-003

## OUTCOME OF PHILADELPHIA POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA IN ADULT PATIENTS – A SINGLE CENTRE EXPERIENCE

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**Background:** In the era of potent tyrosine kinase inhibitor (TKI) and novel immunotherapies, there are doubts whether allo-hemopoietic stem cell transplant (allo-HSCT) is still the best treatment option for Ph+ ALL. We aimed to evaluate the outcome and associated prognostic factors of adult patients with Ph+ ALL treated in Ampang Hospital, a national referral centre in Malaysia.

**Methods:** Data was retrospectively collected and analysed for all adult patients ( $\geq 12$  years) with Ph+ ALL who undergone treatment from 2006 till 2018.

**Results:** here were 96 adult patients, diagnosed with Ph+ ALL. Median age of diagnosis was 37 years with slightly more female to male.

The commonly used chemotherapy regimen were GMALL/BFM inspired protocol (51%, n=49) and HyperCVAD protocol (49%, n=47) in combination with TKI. The remission post induction rate was 83% with relapse rate of 37.0%. Induction death was approximately 4.3% (n=4). Thirty-eight patients (39.6%) proceeded to allo-HSCT. At the time of analysis, 33 patients (34.4%) had survived. Median OS and EFS time was 16 months and 11 months. The 3-year OS and EFS was 29.5% and 28.4% respectively. Multivariate analysis also showed that 3-log reduction of BCR-ABL levels from after consolidation week16 (HR= 2.359, P=0.047; HR=2.440, P= 0.049) conferred to better 3 year OS and EFS .

Amongst the transplant cohort (n=38), 16 (42.1%) of them died due to disease progression/relapsed (50%), infection (31.1%) or other transplant related mortality (7.9%) such as GVHD(n=2) and VOD(n=1). Transplant in CR>1 (HR=3.787, P=0.033) and less than 3-log reduction of BCR-ABL pre-transplant eg. level of >0.1% (HR= 4.106, P=0.022) were independent prognostic factor for inferior OS

**Conclusion:** In a resource constrained setting such as Malaysia, allo-SCT is still preferably as it confer survival advantage and considered a relatively affordable procedure; as oppose to the financial burden imposed by novel therapies. .

**Keywords:** Philadelphia chromosome-positive, acute lymphoblastic leukemia, outcome, allogeneic stem cell transplantation

## MRD POSTIVE AFTER ALLOGENETIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IS NOT A POOR PREDICTOR OF OUTCOME FOR PHILADELPHIA CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

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**Purpose or Background:** Total 116 cases of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) underwent allogeneic hematopoietic stem cell transplantation(HSCT) in Lu Daopei hospital from 2012 to 2017

**Method or Case:** The minimal residual disease(MRD) was measured with the real-time PCR method or flow cytometry. There were haplo relative(n=77), identical sibling donor (n=21) and urelated donor (n=18) transplant respectively. All patients reached complete remission before HSCT. 44 patients were MRD negative before HSCT and other 72 cases were MRD positive. The median age was 20 years. 104 patients received total body irradiation(TBI) conditioning regime, whereas 12 patients received Busulphan based regimen.

**Results or Progress:** The 5 years overall survival was 73.2%. Top 4 causes of death were GVHD, infection, relapse and TMA. Frequency of 100 days aGVHD was 44.3% and frequency of > 2 grade aGVHD was 8.8%. The 5-year overall survival for the MRD negative, MRD positive, bone marrow and extramedullary relapse after HSCT was 74.4%, 90.9% , 38.1% and 66.7%. All patients who were MRD positive post transplant received preemptive therapy for relapse prevention. The therapy include reduction of immunosuppressants, TKI drugs, chemotherapy and cells therapy.

**Conclusion or Discussion:** Our result indicate that MRD positive after HSCT in Ph+ALL patients is not a poor predictor of outcome.

**Keywords:** Philadelphia chromosome-positive acute lymphoblastic leukemia, allogeneic hematopoietic stem cell transplantation

## THE QUANTIFICATION OF MINIMAL RESIDUAL DISEASE PRE- AND POST-UNMANIPULATED HAPLOIDENTICAL ALLOGRAFT BY MULTIPARAMETER FLOW CYTOMETRY IN PAEDIATRIC ACUTE LYMPHOBLASTIC LEUKAEMIA

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**Purpose or Background:** This study aimed to determine the impact of the pre- and post- minimal residual disease (MRD) status as well as the peri-transplant MRD kinetics on clinical outcomes in paediatric ALL patients who received haploidentical allografts.

**Method or Case:** A retrospective study (n=166) was performed. MRD was determined using multiparameter flow cytometry.

**Results or Progress:** Paediatric ALL patients with pre-MRDneg had a lower cumulative incidences of relapse (CIR) compared to those with pre-MRDpos (19.7% vs. 41.2%, P=0.009). Compared to post-MRDneg group, patients with post-MRDpos experienced higher CIR (81% vs. 15.9%, P < 0.001) and inferior LFS (14.3% vs. 66.9%, P < 0.001) and OS (19.1% vs. 66.9%, P < 0.001). In regard to peri-MRD kinetics, compared with the MRD-decreasing group and MRDneg/MRDneg group, MRD-increasing group had higher CIR, worse probabilities of LFS and OS (P < 0.001). Compared to pre-MRDneg/post-MRDneg group, a higher CIR was found in the pre-MRDpos/post-MRDpos group (66.7% vs. 12.5%, P < 0.001), pre-MRDpos/post-MRDneg group (32.0% vs. 12.5%, P = 0.016) and pre-MRDneg/post-MRDpos group (91.7% vs. 12.5%, P < 0.001). A lower incidence of LFS and OS were found in pre-MRDpos/post-MRDpos group and pre-MRDneg/post-MRDpos group than in pre-MRDneg/post-MRDneg group (P < 0.05). Multivariate analyses confirmed the association of pre-MRD status, post-MRD status and peri-MRD kinetics with outcomes (P < 0.05).

**Conclusion or Discussion:** The results indicate that, in the paediatric ALL subgroup, not only pre-MRD status or post-MRD status but also peri-SCT MRD dynamics, were associated with an increased CIR after haploidentical allografts. Peri-transplant MRD kinetics could allow better relapse stratification.

**Keywords:** paediatric acute lymphoblastic leukaemia, allogeneic stem cell transplantation, minimal residual disease, multiparameter flow cytometry, unmanipulated haploidentical allografts



## STUDYING THE EFFECTS OF METHOTREXATE ON HEMATOPOIESIS AND NF-kB PATHWAY USING IN VITRO AND IN VIVO MODEL SYSTEMS

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**Purpose or Background:** Methotrexate (MTX) is an anti-folate and an anti-cancer drug used as chemotherapy for different types of cancers including leukemia. It is also an immunosuppressant exhibiting side effects such as nausea, vomiting, liver disease, lung disease and lymphoma. We are interested in understanding the effects of MTX on hematopoietic signaling pathways. Existing reports suggest that MTX activity interferes with the tumorigenic pathways.

**Method or Case:** In the current study, we are using in vivo (*Drosophila melanogaster*, mouse) and in vitro (K562 myeloid leukemia cell line) models to decipher the effect of MTX on hematopoietic tumors. Immunofluorescence assay was used to examine the NF-kB localization. TLR2 and COX1 transcripts were analyzed by real time PCR and protein level of NF-kB was measured by western blot. We have studied the effects of MTX on NF-kB pathway specifically in both the blood cells and cancerous blood cells.

**Results or Progress:** Since NF-kB is known to be involved in both proliferation and inflammation of blood cells. Our preliminary results using *Drosophila* model showed that MTX inhibits nuclear localization of NF-kB by cytoplasmic retention. While MTX is known to down-regulate NF-kB pathway, in vitro studies using leukemia cells (K562) showed that prolonged treatment with MTX leads to up-regulation of the transcripts of TLR2 and COX1.

**Conclusion or Discussion:** Prolonged treatment of MTX increases the NF-kB protein expression in leukemia cells.

Our findings reveal an opposite role of MTX on modulating NF-kB signaling pathway upon prolonged treatment.

**Keywords:** NF-kB, MTX, signaling, blood, leukemia, cancer

PP-007

## AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION FOR CORE-BINDING FACTOR-ACUTE MYELOID LEUKEMIA IN FIRST COMPLETE REMISSION: A PHASE 2 PROSPECTIVE TRIAL

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**Purpose or Background:** Core-binding factor (CBF)-acute myeloid leukemia (AML) including t(8;21); RUNX1-RUNX1T1 and inv(16) or t(16;16); CBFB-MYH11 is considered to have a favorable prognosis. However, approximately 50% of patients experience disease relapse during or after post-remission therapy, which generally consists of repeated cycles of high-dose cytarabine (HDAC). There have been several studies demonstrating that autologous hematopoietic cell transplantation (AHCT) was associated with improved survival and decreased relapse rate. In this prospective study, we aimed to evaluate the efficacy of AHCT in patients with CBF-AML in the first complete remission (CR1).

**Method or Case:** Patients with CBF-AML achieving CR1 after induction chemotherapy and planning to receive HDAC consolidation chemotherapy between 15 and 65 years of age were eligible for the study. Autologous peripheral blood stem cells were collected during the first or second course of HDAC, and conditioning regimen for AHCT included busulfan (3.2 mg/kg/day, days -7 to -5) and etoposide (400 mg/m<sup>2</sup>/day, days -3 to -2).

**Results or Progress:** Between May 2010 and April 2018, twenty-nine patients received AHCT. The median age was 40 years (range, 19–60), and 17 (58.6%) and 12 patients (41.4%) had t(8;21) and inv(16), respectively. At the time of AHCT, 10 (34.5%) and 15 patients (51.7%) showed undetectable and positive measurable residual disease with quantitative PCR. All patients achieved neutrophil engraftment after median 12 days. After a median follow-up of 4.7 years, the estimated 5-year overall survival, event-free survival, relapse, and non-relapse mortality incidences were 89.0%, 82.5%, 17.5%, and 0%, respectively. There was no significant difference in outcomes between the two types of CBF mutation.

**Conclusion or Discussion:** In conclusion, AHCT as a post-remission therapy for CBF-AML in CR1 is feasible in terms of favorable survival outcomes with low relapse rate. Further studies are needed to establish an optimal post-remission therapeutic strategy for CBF-AML.

**Keywords:** Core-binding factor, Acute myeloid leukemia, Autologous hematopoietic cell transplantation, Post-remission

## MISMATCH BETWEEN LEUKEMIA AND LYMPHOMA DISEASE BURDEN AND CLINICAL TRIALS BEING CONDUCTED IN INDIA FOR THESE DISEASES: A CROSS SECTIONAL STUDY

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**Purpose or Background:** Research output of any country should be as per the research need of that country. Clinical trials happening in a country for a particular disease is one of the parameter for measurement of research output for that disease in the country. India is becoming attractive destination for clinical trials but there is no data available to see the relationship between clinical trial happening for leukaemia and lymphomas/multiple myeloma and disease burden of these diseases in India. This study was designed to evaluate relationship between disease burden of leukaemia and lymphomas/ multiple myeloma and clinical trials conducted for these diseases in India.

**Method or Case:** The data related to clinical trials happening in India was downloaded from the website of Clinical Trial Registry of India (<http://ctri.nic.in>) and data related to the disease burden of the India was extracted from the website of World Health Organization (WHO). Mortality, Disease Adjusted Life Years (DALYs), Years Lost Due to Disability (YLD) and Years of Life Lost (YLL) were the disease burden parameters and these parameters were compared with the frequencies of the clinical trials registered in the registry for leukaemia and lymphomas/multiple myeloma.

**Results or Progress:** Out of total 3928 clinical trials registered in clinical trial registry of India, 32 (0.81%) were related to the different leukaemia while mortality due to leukemia was 0.29% of total mortality, DALYs due to leukemia was 0.28% of total, YLDs due to leukemia was 0.02% of total and YLL was 0.37% of total YLLs. 0.63% trials were related to the lymphoma/multiple myeloma while total mortality, DALYs, YLDs, YLLs were 0.30%, 0.22%, 0.02% and 0.3% respectively.

**Conclusion or Discussion:** Frequency of clinical trials related to leukemia and lymphoma/multiple myeloma are more compared to disease burden of these diseases in India.

**Keywords:** Leukaemia, Lymphoma, Clinical Trials, Disease Burden, India

## SAFETY AND EFFICACY OF THROMBOPOIETIN MIMETICS IN PATIENTS WITH MYELODYSPLASTIC SYNDROMES: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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**Purpose or Background:** Thrombocytopenia is common problem in patients with myelodysplastic syndromes (MDS) and is associated with bleeding complications, occasionally life-threatening. Thrombopoietin (TPO) mimetics considered as an alternative therapy for MDS patients with thrombocytopenia. The objective of this study aimed to evaluate the efficacy and safety of TPO mimetics in patients with MDS.

**Method or Case:** MEDLINE and CENTRAL databases were searched to identify English language articles from inception to May 2019. Eligible randomized controlled trials (RCTs) evaluating the efficacy and safety of TPO mimetics comparing with a control group. The outcome measures were; mortality, incidence of bleeding, platelet transfusion rates, risk of progression to acute myeloid leukaemia (AML). A random effects model was used to calculate the risk ratio (RR) with 95% confidence interval (CI).

**Results or Progress:** A total eight randomized controlled trials (RCTs) with 930 participants included, five receiving romiplostim and three receiving eltrombopag. Follow up was ranged from 4-58 weeks. Results from meta-analysis showed romiplostim (RR 0.92, 95% CI 0.86 to 0.99) and eltrombopag (RR 0.37, 95% CI 0.20 to 0.69) significantly decreased the incidence rate of bleeding. No significant difference was observed in increased rate of AML progression, when TPO mimetics compared to placebo (RR 1.08, 95% CI 0.66 to 1.76). However, eltrombopag little or non-significantly reduce the rate of AML progression (RR 0.81, 95% CI 0.66 to 1.00; p=0.05). There was no significant difference observed that TPO mimetics significantly decreased the rate of platelet transfusion (RR 0.98, 95% CI 0.67 to 1.43) and mortality rate (RR 1.02, 95% CI 0.82 to 1.27).

**Conclusion or Discussion:** The TPO mimetics did not reduce the AML progression and mortality rate. However, romiplostim and eltrombopag significantly decreased the incidence rate of bleeding. Further, RCTs with long term follow-up and real world studies required to robust the present findings.

**Keywords:** romiplostim, eltrombopag, myelodysplastic syndromes, thrombocytopenia, safety, meta-analysis

## THE INCIDENCE, RISK FACTORS, AND OUTCOMES OF PRIMARY PROLONGED ISOLATED THROMBOCYTOPENIA AFTER HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Purpose or Background:** The aim of this study was to evaluate the incidence, risk factors, and outcomes of primary prolonged isolated thrombocytopenia (PT) after haploidentical hematopoietic stem cell transplantation (haplo-HSCT).

**Method or Case:** We retrospectively analyzed patients who received haplo-HSCT for various hematologic malignancies at Peking University Institute of Hematology between January 2015 and December 2016. Of the 918 patients, 93 (10.1%) developed primary PT. We designed a propensity score method-based study. For each primary PT patient, control subjects (1:3) were selected using the propensity score matching method in R.

**Results or Progress:** Total of 372 recipients were enrolled in the study: 93 in PT group and 279 in the control group. Multivariate analysis showed that patients older than 25 years ( $P=0.002$ ), median mononuclear cells ( $P=0.000$ ), median CD34+ counts ( $P=0.003$ ), history of grade II–IV acute graft versus host disease (GVHD) ( $P=0.000$ ) and EBV infection after haplo-HSCT ( $P=0.016$ ) were independent risk factors for primary PT. Primary PT was significantly associated with higher transplant-related mortality (TRM,  $P<0.001$ ), inferior overall survival ( $P=0.001$ ) and progression-free survival ( $P=0.005$ ).

**Conclusion or Discussion:** In conclusion, the incidence of primary PT following haplo-HSCT was 10.1%. Primary PT was associated with poorer survival and higher TRM along with old age, grade II–IV acute GVHD, and EBV infection after haplo-HSCT.

**Keywords:** prolonged isolated thrombocytopenia, haploidentical, hematopoietic stem cell transplantation

## IMPACT OF ANTI-THYMOCYTE GLOBULIN DOSES IN UNRELATED HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PATIENTS WITH MYELOID NEOPLASM

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**Background:** Anti-thymocyte globulin (ATG) is widely used for the prophylaxis of graft-versus-host disease (GVHD) in hematopoietic stem cell transplantation (HSCT). However, there is still controversy regarding the optimal dose of ATG.

**Method:** This was a retrospective multi-center study that assessed the impact of ATG doses in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) undergoing an unrelated HSCT. The patients who received peripheral blood stem cells (PBSC) transplantation after conditioning regimens containing i.v. busulfan (BU), fludarabine and rabbit ATG between 2010 and 2017 were included.

**Results:** A total of 96 patents with AML (n=74) or MDS (n=22) were included in our analyses. 66 patients (69%) received a myeloablative regimen (i.v. BU>6.4 mg/kg). Low-ATG (ATG 3 mg/kg), intermediate-ATG (ATG 4.5-5 mg/kg) and high-ATG (ATG 9 mg/kg) were given in 36, 49 and 11 patients, respectively. The rate of 2-year relapse-free survival was significantly higher in the intermediate-ATG group than other groups (33.3% in the low-ATG group, 62.4% in the intermediate-ATG group, and 27.3% in the high-ATG group, p=0.034). The rate of chronic GVHD-free and relapse-free survival at 2 years was significantly higher in the intermediate-ATG group (16.7% in the low-ATG group vs. 52.7% in the intermediate-ATG group, and 18.2% in the high-ATG group, p=0.001). The rate of 2-year overall survival in each group did not differ significantly (43.5% in the low-ATG group, 68.3% in the intermediate-ATG group, and 45.5% in the high-ATG group, p=0.079).

**Conclusion:** Our study shows that the incidence of extensive chronic GVHD was similar regardless of the doses of ATG after transplantation of PBSC from unrelated donor for patients with AML or MDS. However, the rate of relapse-free survival and the rate of a composite end point chronic GVHD-free and relapse-free survival were significantly higher in the intermediate dose (4.5-5 mg/kg) of ATG group.

**Keywords:** ATG, unrelated HSCT, GVHD

## IMPACT OF BONE MARROW-DERIVED MESENCHYMAL STROMAL CELLS ON HEPATIC FIBROSIS AMONG CLASS III *B* THALASSEMIA MAJOR PATIENTS RECEIVING AN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Background & Aims:** Beta-thalassemia major is a severe early-onset form of inherited disorders characterized by a genetic deficiency in the synthesis of beta-globin chains requiring regular red blood cell transfusions. Patients with beta-thalassemia major often develop liver fibrosis due to liver iron overload. The only potentially curative option for these patients is allogeneic hematopoietic stem cell transplantation (HSCT). However, even if these patients have a successful HSCT, the liver iron overload will not decrease and hepatic fibrosis may still progress. Mesenchymal stem cells (MSCs) are part of the most important population of stem cells that are believed to play an important role in the repair of damaged tissues. However, so far the role of MSCs in liver fibrosis is still controversial. The present study is aimed to investigate whether MSCs can alleviate liver fibrosis after HSCT in beta-thalassemia major patients.

**Methods:** The study comprised 38 patients matched for age and sex with class III beta-thalassemia major who had an indication for HSCT at Hematology, Oncology and Stem Cell Transplant Research Center (HORCSCT), Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran between May 1998 and November 2017. These patients were randomly assigned to receive co-transplantation with bone marrow-derived MSCs (n = 19), or transplantation without bone marrow-derived MSCs (n = 19). MSCs were obtained from a donor's bone marrow and co-transplanted at a dose of 1-2 x10<sup>6</sup> four hours before HSCT. An ultrasound-guided liver biopsy, FibroScan and T2\*-Weighted Magnetic Resonance Imaging (T2\* MRI) were performed in all patients before and one year after HSCT to assess the effect of bone marrow-derived MSCs on hepatic fibrosis.

**Results:** Finally, a total of 38 patients (21 male, 17 female; mean age: 21.54 ± 8.48 years) completed the study in two groups. No significant side-effects and complications were observed in both groups of patients. There was a significant reduction in the liver pathologic change in patients co-transplanted with bone marrow-derived MSCs compared with patients transplanted with HSC alone (P = 0.001). Co-transplantation with bone marrow-derived MSCs significantly improved focal (spotty) lytic and confluent necrosis. The findings of the FibroScan showed that liver stiffness measurements based on the METAVIR scoring system in patients transplanted with HSC-MSC transfusion compared with patients transplanted with HSC alone (P =

0.02). There was no relation between hepatic steatosis using a controlled attenuation parameter (CAP) in both groups of patients ( $P = 0.65$ ). In addition, the findings of the T2\* MRI showed that there was no significant reduction in hepatic and cardiac iron load between the two groups.

**Conclusion:** Our study demonstrated that co-transplantation of hematopoietic stem cells with MSCs alleviates liver fibrosis after HSCT in beta-thalassemia major patients, but further research is needed to confirm the findings.

**Keywords:** Mesenchymal stem cells, Liver fibrosis, Thalassemia major, Co-transplantation



## CLINICAL ANALYSIS OF AUTOIMMUNE HEMOLYTIC ANEMIA AFTER UNRELATED ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN THALASSEMIA MAJOR

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**Purpose:** To explore the diagnosis, treatment and prognosis of autoimmune hemolytic anemia (AIHA) after unrelated allogeneic hematopoietic stem cell transplantation in patients with thalassemia major (TM).

**Methods:** A retrospective analysis of the AIHA status was conducted in 62 TM patients after MUD-HSCT from July 2014 to December 2018. The direct and indirect Coombs test and hemolysis were monitored.

**Results:** There were 12 cases with Coombs test(+), among which 8 cases were ABO incompatible. Four of the 62 TM patients (6.45%) were diagnosed with post-transplant AIHA. The median time of AIHA was 10 (8-12) months after HSCT. All post-transplant AIHA patients were positive in direct and indirect Coombs test, the main clinical manifestations were dizziness, fatigue, pale complexion skin and sclera yellow, and soy sauce urine. Two patients were effectively treated with methylprednisolone and cyclosporine. However, another two patients had no response to corticosteroids, plasma exchange, cyclophosphamide and rituximab. Then, the Bortezomib was used in the two patients at 1.3 mg/m<sup>2</sup> subcutaneously at D1, 4, 8, and 11 (4-8 doses), and their hemoglobin rose to the normal level and the DAT became negative.

**Conclusions:** The incidence of AIHA was 6.54% in TM patients after unrelated allo-HSCT. Monitoring of the Coombs test was important for diagnosis. The prednisolone plus cyclosporine treatment is effective, and treatment with bortezomib was effective strategy for refractory post-transplant AIHA.

**Keywords:** Hematopoietic stem cell transplantation, Autoimmune hemolytic anemia, Thalassemia, Glucocorticoid, Rituximab, bortezomib

PP-015

## COMPARABLE OUTCOMES BETWEEN HSCT FROM HAPLOIDENTICAL AND MATCHED RELATED DONOR OR UNRELATED DONOR FOR SAA PATIENTS AGED $\geq 40$ YEARS: A MULTICENTER COHORT STUDY

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**Purpose:** This study aimed to confirm the outcome of haploidentical haematopoietic stem cell transplantation (HID-HSCT) in severe aplastic anemia(SAA) patients  $\geq 40$  years.

**Method:** We conducted a multicenter cohort study to analyze the outcome of HSCT in acquired SAA patients aged  $\geq 40$  years in 2 centers and make comparison between outcome of HID-HSCT and HSCT from a matched sibling donor (MSD) and an unrelated donor (URD) in the same period.

**Results:** With a median follow-up time of 17.6 months, 85 consecutive SAA patients undergoing HSCT, including 35 receiving HID-HSCT, were enrolled in the study; the median patient age was 45 years (40,58). All patients achieved myeloid engraftment except one died on day +10 and the cumulative engraftment rate of platelets was  $92.9 \pm 0.1\%$ . The cumulative incidence rate of Grade II~IV acute graft versus host disease (aGvHD) and chronic graft versus host disease (cGvHD) at 3 year was  $14.1 \pm 0.1\%$  and  $17.3 \pm 0.2\%$ . At 3 years, the overall survival(OS) and failure-free survival(FFS) rates were  $91.2 \pm 3.2\%$  and  $89.7 \pm 3.5\%$ , respectively. In multivariate analysis, the only factor associated with inferior survival was ECOG-Score  $\geq 2$  (OS 95.3% vs 66.7%  $p=0.026$ , HR 8.19). HID-HSCT was associated with a heavier transfusion burden, longer intervals from diagnosis to HSCT and a higher incidence of Grade II~IV aGvHD and cGvHD. The OS rate at year 3 was  $86.7 \pm 6.4\%$  in HID cohort, which was similar to the incidences of the MSD( $92.1 \pm 4.4\%$ ,  $p=0.746$ ) and URD(100%,  $p=0.234$ ) cohorts.

**Conclusion:** HID-HSCT achieved a comparable outcome with HSCT from MSD and URD and it might be a feasible treatment for SAA patients aged  $\geq 40$  years without MSD.

**Keywords:** Severe Aplastic Anemia, Hematopoietic Stem Cell Transplantation, Elderly, Haploidentical transplantation

## MOBILIZATION OF BONE MARROW-DERIVED STEM CELLS IS NOT SUFFICIENT TO PREVENT GRAFT DYSFUNCTION IN RENAL ALLOGRAFT RECIPIENTS

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**Background:** Bone marrow-derived stem cells (BMSCs) can be mobilized into circulation during tissue injury and contribute to parenchymal restoration. The present work was designed to study the relation between mobilization of BMSCs into peripheral blood after renal transplantation and their relation to graft dysfunction.

**Methods:** Thirty patients with renal transplantation for more than 6 months [15 patients with stable renal function and 15 patients with chronic allograft dysfunction (CAD)] and 15 healthy subjects were included in the study. Hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) in fresh blood samples were identified as CD34+CD45+CD117+ and CD34-CD45-CD106+ cells respectively using flow cytometric assay. Serum levels of stem cell factor (SCF), a mobilizing factor, and high sensitivity C-reactive protein were measured using enzyme linked immunosorbant assay. Renal function was assessed by measuring serum creatinine, estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine (UAC) ratio. Doppler ultrasonography was done to study renal hemodynamics. Renal biopsy was performed in patients with CAD to assess staging and degree of fibrosis.

**Results:** The number of circulating HSCs and MSCs and serum SCF levels were significantly higher in allograft recipients with and without CAD than healthy subjects and in patients with CAD than in patients with stable renal function ( $P < 0.01$ ). The number of mobilized BMSCs showed positive correlations with serum levels of SCF, hsCRP and creatinine, UAC ratio and resistive and pulsatility indices and inverse correlations with eGFR and renal blood flow ( $P < 0.05$ ) although they were not correlated with degree of fibrosis in renal biopsies ( $P > 0.05$ ).

**Conclusion:** BMSCs are mobilized into circulation in renal allograft recipients possibly in response to inflammation although this was not sufficient to prevent graft dysfunction. Future studies are needed to investigate whether BMSC therapy can enhance graft survival and recovery of CAD after renal transplantation.

**Keywords:** Bone Marrow-Derived Stem Cells, Renal Transplantation, Chronic Allograft Dysfunction

PP-017

## POST-TRANSPLANT CYCLOPHOSPHAMIDE VERSUS ANTITHYMOCYTE-GLOBULIN IN HLA-MATCHED UNRELATED TRANSPLANTATION FOR HEMATOLOGIC MALIGNANCIES: SINGLE-CENTER EXPERIENCE

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**Background:** Post-transplant cyclophosphamide (PTCy) and antithymocyte-globulin (ATG) are the most commonly used regimens for the prophylaxis of graft-versus host disease (GVHD). We compared these two regimens in HLA-matched unrelated donor (MUD) transplantation for hematologic malignancies.

**Method:** We retrospectively analyzed the consecutive adult patients with hematologic malignancies who received MUD transplantation at Chungnam National University Hospital between January 2013 and January 2019. Patients who received second transplantation and had refractory disease were excluded.

**Results:** This study included 34 patients (12 and 22 patients in PTCy and ATG group, respectively). Median age was 56 years old in PTCy group and 48.5 years old in ATG group. Follow-up duration was longer in ATG group (median 40 months, ranged from 3 to 60 months) than in PTCy group (median 19 months, ranged from 3 to 34 months,  $p=0.006$ ). The 20-months overall survival rate were 75.0% in PTCy vs. 81.6% in ATG ( $p=0.792$ ), the 20-months relapse rate were 41.7% in PTCy vs. 34.3% in ATG ( $p=0.491$ ). The cumulative incidence of grade 2 to 4 acute GVHD were 16.7% in PTCy vs. 30.6% in ATG ( $p=0.551$ ), and the 20-month limited and extensive chronic GVHD rate were 59.1% in PTCy vs. 78.8% in ATG ( $p=0.718$ ), and the 20-month extensive chronic GVHD rate were 12.5% in PTCy vs. 16.7% in ATG ( $p=0.718$ ). Neutrophil engraftment time was similar in both group [median(range); 15.0(12.0-17.0) days in PTCy vs. 14.0(12.0-19.0) days in ATG,  $p=0.961$ ]. The incidence of cytomegalovirus reactivation did not differ in both group [5(41.7%) patients in PTCy vs. 7(31.8%) patients in ATG,  $p=0.566$ ]. However, The cost of ATG was much more expensive than PTCy [median(range); 4,834,285(2,636,883-7,910,649) Korean Won in ATG vs. 61,740(51,450-82,320) Korean Won in PTCy,  $p<0.001$ ].

**Conclusion:** PTCy have similar clinical outcomes compared with ATG in HLA-matched unrelated donor transplantation and PTCy is more cost-effective than ATG.

**Keywords:** Post-transplant Cyclophosphamide, Antithymocyte-globulin, Hematopoietic stem cell transplantation, Graft-versus host disease

## CONDITIONING REGIMEN WITH CYCLOPHOSPHAMIDE AND DE-ESCALATED TOTAL BODY IRRADIATION WITH 400 cGY FROM 600 cGY FOR SEVERE APLASTIC ANEMIA: PILOT STUDY

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**Purpose or Background:** Stem cell transplantation from an unrelated donor (URD-SCT) is often considered in patients with severe aplastic anemia (SAA) whom immunosuppressive therapy failed and matched sibling donor is not available. This pilot study explored the feasibility and safety of conditioning regimen with cyclophosphamide (50mg/kg for 2 days) plus 400 cGy total body irradiation (TBI400-Cy, pilot-group) compared to historical conditioning regimen with cyclophosphamide plus 600 cGy total body irradiation (TBI600-Cy, historical-group) in SAA patients who received URD-SCT.

**Method or Case:** Clinical outcomes of three patients in pilot-group were compared to 15 patients in historical group. For graft-versus-host-disease prophylaxis, rabbit ATG was administered with a dose of 5mg/kg in pilot-group and that of 2.5mg/kg in historical-group. Except for one patient who received bone marrow stem cell in historical-group according to donor's preference, all patients received mobilized-peripheral blood stem cell.

**Results or Progress:** With median follow-up of 5.3 (range, 2.1-8.1) months in pilot-group and 29.4 (range, 0.9-49.0) months in historical group, Engraftments of neutrophil (median 11 days for both groups) and platelet (median 12 days for historical-group vs. 11 days for pilot-group) were achieved in all patients. All patients of pilot-group alive without graft failure whereas one patient of historical-group died of refractory acute GVHD. Compared to cumulative incidences of grade acute II-IV GVHD rates with 33.3% (95% CI, 7.7-50.5) at day+180 in historical cohort, there were no patients who presented grade II-IV acute GVHD until follow-up.

**Conclusion or Discussion:** In this pilot study, de-escalated TBI with 400 cGy with cyclophosphamide has shown to be safe, and well to be tolerated in SAA patients treated with URD-SCT. Large number of patients and long-term follow-up are needed to confirm the feasibility of this approach.

**Keywords:** Comorbidity, stem cell transplantation, severe aplastic anemia, total body irradiation

## THE COMPARISON OF TWO PROPHYLACTIC DLI STRATEGIES FOR PREVENTION OF RELAPSE IN ADVANCED ACUTE LEUKEMIA UNDERGOING ALLO-HSCT

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**Purpose or Background:** Prophylactic donor lymphocyte infusion (pDLI) is regarded as the effective strategy to reduce relapse in advanced acute leukemia undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT), but the optimal timing remains uncertain. Our previous strategy of sequential intensified conditioning followed by pDLI on day +60 regardless of minimal residual disease (MRD) could reduce relapse but had high graft-versus-host disease (GVHD). To reduce GVHD after pDLI, we modified this strategy mainly by delaying the time of pDLI to day +90 unless MRD was positive on day +60.

**Method or Case:** A total of 78 advanced acute leukemia undergoing allo-HSCT between January 2015 and December 2017 were enrolled in this prospective study, and 83 advanced acute leukemia undergoing allo-HSCT from January 2012 to December 2014 were taken as control.

**Results or Progress:** Sixty-nine patients in the study cohort and 74 patients in the control cohort received pDLI, respectively. The overall and grade III-IV acute GVHD incidences after pDLI were 32.9% (95%CI: 25.3%-40.6%) and 9.1% (95% CI: 5.1%-14.5%), which did not differ significantly between the two cohorts ( $P=0.597$ ,  $P=0.182$ ). The extensive chronic GVHD (cGVHD) incidence after pDLI in the study cohort was lower than that in the control cohort (10.1% vs 27.0%,  $P=0.012$ ). The overall cGVHD incidence and GVHD mortality after pDLI were similar between the two cohorts ( $P=0.337$ ,  $P=0.208$ ). The leukemia relapse rate was also similar between the two cohorts ( $P=0.735$ ). Multivariate analysis revealed that compared with previous pDLI strategy, modified pDLI strategy was associated with a lower risk of extensive cGVHD after pDLI ( $P=0.019$ ), but had no significant effect on relapse ( $P=0.731$ ).

**Conclusion or Discussion:** The strategy of pDLI based on time and MRD post-transplant could reduce the incidence of extensive cGVHD but not increase leukemia relapse for advanced acute leukemia undergoing allo-HSCT.

**Keywords:** prophylactic donor lymphocyte infusion, advanced acute leukemia, relapse, allogeneic hematopoietic stem cell transplantation

## COMPARISON OF POST-TRANSPLANT OUTCOME BY CONDITIONING INTENSITY IN PATIENTS WITH MINIMAL RESIDUAL DISEASE NEGATIVE ACUTE MYELOID LEUKEMIA (MRDnegAML)

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**Introduction:** Recent data emerges that transplantation with reduced intensity conditioning (RIC) seems to be effective as myeloablative conditioning (MAC). However, relapse is a major concern with RIC, and identification of patients at equivalent risk of relapse irrespective of conditioning intensity is needed.

**Method:** Between June 2012 and Jan 2018, a total of 567 AML patients underwent allogeneic hematopoietic stem cell transplantation (HSCT). Among them, we selected 243 patients who fulfilled i) intermediate or poor risk group by NCCN (2017.Version 3), ii) CR or CRi at HSCT, iii) received either MAC (BuCy or CyTBI) or RIC (FluBu2TBI400) transplant from matched sibling donor (MSD) or matched unrelated donor (MUD), and iv) having Wilm's tumor (WT1) gene expression results before transplant.

**Results:** The median WT1 gene expression level (bone marrow) was 56.7 copies/104ABL. When WT1 250 copies/104ABL were used as cut-off value for MRD, 205 out of 243 patients (84.4%) achieved MRDneg complete remission (CR) at transplant. Among these MRDneg CR patients, 164 (80.0%) and 41 (20.0%) patients received MAC and RIC, respectively. As a group, there were more elderly ( $\geq 60$  years) and intermediate risk patients in RIC group whereas no difference was observed between two groups in regard to gender, donor type and anti-thymocyte globulin (ATG) use. Over the median follow up duration of 31.8 months, there was no difference in overall survival (OS), disease free survival (DFS), cumulative incidence of relapse (CIR) and non-relapse mortality (NRM) between MAC and RIC groups ( $p=0.546$ ,  $p=0.766$ ,  $p=0.371$  and  $p=0.277$  for OS, DFS, CIR and NRM). In multivariate analysis adjusted for age, donor type, risk group and ATG use, conditioning intensity was not prognostic for post-transplant relapse or survival in MRDneg CR AML patients.

**Conclusion:** Similar outcomes were observed between RIC and MAC when patients achieved MRDneg complete remission (CR) at transplant.

**Keywords:** acute myeloid leukemia, minimal residual disease, allogeneic transplantation, WT1 gene

PP-021

## GAMMA-DELTA-T CELLS DYNAMICS IN THE RECIPIENTS OF ALLOGENEIC PERIPHERAL BLOOD HEMATOPOEITIC STEM CELL TRANSPLANT (PBHSCT) –A STUDY FROM NORTH INDIAN TERTIARY CARE TEACHING INSTITUTE

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**Background:** Human  $\gamma\delta$ -T cells have been demonstrated to play active role in early responses to infective agents, autoimmune , inflammatory ,allergic disorders and transplant settings. We prospectively studied their trend and impact, if any, on early post transplant phase in Indian settings.

**Method:** Study design/period : Prospective longitudinal study, January 2018-December 2018

**Objectives:**  $\gamma\delta$ -T cells enumeration in allogeneic PBHSCT recipient

**Methodology:**  $\gamma\delta$ -T cells enumeration was done by flowcytometry on the recipients samples collected at baseline , D+28, D+56 and D+100 .

**Results:** Twelve ( PBSC=11; BMSC=1) patients( AML-4, Aplastic Anaemia-4 & CML-1) received allogeneic stem cells during study period. Data for nine cases analysed (mean age 25+/-9.7 years). Mean  $\gamma\delta$ -T cells (% , absolute count/  $\mu$ L) of harvest were  $0.71 \pm 0.8$  and  $2201.13 \pm 3443.79$  respectively .Mean  $\gamma\delta$ -T cells( % ) in the recipient showed decline from baseline( $0.48 \pm 0.63$ ) to ( $0.29 \pm 0.31$ ) on D+28 followed by rise by D+56 ( $0.77 \pm 0.89$ ) thereafter declining towards D+100 ( $0.7 \pm 0.51$ ) but remaining above the baseline ( $p=0.2$ ). There was increase in mean absolute  $\gamma\delta$ -T cells( / $\mu$ L) from baseline( $10.98 \pm 12.97$ ) through D+28 ( $20.98 \pm 29.6$ ) D+56 ( $51.72 \pm 54.51$ ) and some decline on D+100( $37.14 \pm 37.9$ ) but maintained above baseline ( $p=0.423$ ). Two died of culture positive sepsis during study period at D+7 and D+27 respectively with no significant correlation between mortality &  $\gamma\delta$ -T cells counts in their peripheral blood and harvest( $p=0.5$ ). One case relapsed at D+30.  $\gamma\delta$ -T cells counts in peripheral blood and harvest had negative correlation (non significant) with duration of hospital stay (Spearman correlation  $r = -0.332$ ;  $p=0.38$  &  $r = -0.209$ ;  $p=0.58$  respectively). None developed GVHD till D+100.

**Conclusion :**  $\gamma\delta$ -T cells % and absolute count reached nadir by D+28 but demonstrated gradual rise by D+100 remaining above baseline values without any significant impact on post transplant events. Being a small study results cannot be generalised. A larger study is needed for meaningful conclusion.

**Keywords:**  $\gamma\delta$ -T cells, Allogeneic stem cell transplant, GVHD, sepsis



## EFFECT OF MESENCHYMAL STROMAL CELLS ON T CELLS AFTER ALLOGENIC BONE MARROW PLANTATION

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Bone marrow transplantation (BMT) represents a curative treatment for various hematological disorders. In order to eliminate cancer cells, a large amount of anti-cancer drug should be administered before BMT. During this cytotoxic conditioning procedure, not only cancer cells but also hematopoietic stem cells in the BM and thymic epithelial cells would be damaged. T cells express a receptor with the potential to recognize diverse antigens from pathogens, tumors, and the environment and also maintain immunological memory and self-tolerance. As a result, delayed reconstitution of thymus causes delayed de novo thymopoiesis and lack of T cell-mediated immunity after BMT. Recently, it was reported that several cytokines improve thymopoiesis and immune function after BMT, e.g., RANK ligand, interleukin (IL)-22, IL-7 or stem cell factor. In this study, we evaluated the effect of co-transplantation of tonsil-derived mesenchymal stem cells (T-MSCs) on thymopoiesis and immune function using mouse BMT model. We found that co-transplantation of T-MSCs with BM cells together has better weight recovery rate and larger thymus size than those of BMT only group. T-MSCs showed high level of expression of the factors associated with thymus regeneration (FGF7, IL-15 and FLT3L). These data demonstrate the beneficial effect of T-MSCs in regeneration of the thymus and immune restoration after BMT.

This work was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI18C2392).

**Keywords:** bone marrow transplantation, mesenchymal stromal cell, t cell, thymus

## CLINICAL SIGNIFICANCE OF INCREASED CIRCULATING HEMATOPOIETIC AND MESENCHYMAL STEM CELLS IN PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION

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**Background:** Bone marrow-derived stem cells (BMSCs) are undifferentiated cells characterized by self-renewal and differentiation into multiple cellular population to promote tissue regeneration. The present work was designed to study the frequency of circulating hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) in patients with chronic hepatitis C (CHC) and their relation to hepatic inflammation and fibrosis.

**Methods:** Thirty treatment-naïve patients with CHC and 15 healthy controls were included in the study. Peripheral blood HSCs and MSCs were identified as CD34+CD45+CD117+ and CD34-CD45-CD106+ cells respectively using flow cytometric assay. Serum levels of stem cell factor (SCF), a stem cell mobilizing factor, were determined using enzyme linked immunosorbant assay. Serum aspartate and alanine aminotransferases (AST and ALT) were measured and fibrosis scores [AST-to-platelet ratio index (APRI) and fibrosis-4 (FIB-4) index] were calculated. Liver biopsies were examined to assess METAVIR histological activity grade and fibrosis stage and immunostaining of alpha smooth muscle actin, a marker for activated hepatic stellate cells (HpSCs).

**Results:** Patients with CHC showed significant increases in the frequency of circulating HSCs and MSCs and serum SCF levels compared with healthy controls unrelated to viral load ( $P < 0.05$ ). Based on the frequency of BMSCs in peripheral blood, patients with CHC were distinguished as BMSC mobilizers in 18 (60%) patients and as BMSC non-mobilizers in 12 (40%) patients. BMSC mobilizers showed significantly higher serum SCF levels and significantly lower serum AST and ALT levels, histological activity grade, fibrosis stage, APRI score and intensity of activated HpSCs than BMSC non-mobilizers ( $P < 0.05$ ).

**Conclusion:** Chronic HCV infection is associated with mobilization of BMSCs from bone marrow into the circulation, which may play a role in amelioration of hepatitis C virus-related liver injury. Further studies are needed to investigate the effect of BMSC therapy in local tissue repair during chronic liver diseases.

**Keywords:** Hematopoietic stem cells, Mesenchymal stem cells, Hepatitis C virus, Hepatic fibrosis

## DELETION OF WNTLESS IN COL1A1-EXPRESSING CELLS INDUCES PROGRESSIVE SENESCENCE OF HEMATOPOIETIC STEM CELLS UNDER PREFERENTIAL IMPAIRMENT OF THE BONE MARROW ENVIRONMENT

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**Purpose or Background:** Wnt signaling plays an important role in the process of bone formation and homeostasis and serves as a niche to maintain the functional integrity of stem cells. However, the specific role played by Wnt signaling in bone marrow (BM) microenvironment for the maintenance of BM-conserved hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) remains unclear.

**Method or Case:** To evaluate Wntless (Wls) deficiencies in type I collagen-expressing cells (Col1a1), Col1a1(2.3kb)-Cre mice were crossed with Wls<sup>fl/fl</sup> mice to generate Col1a1(2.3kb)-Cre;Wls<sup>fl/+</sup> male mice. Wls<sup>fl/fl</sup> littermates were used as controls for same-age and same-sex mutant Col1a1(2.3kb)-Cre;Wls<sup>fl/fl</sup> (Wls<sup>col</sup>) mice.

**Results or Progress:** In this study, we investigated how Wnt signaling modulates the BM microenvironment and BM-conserved stem cells using mice with tissue-specific knockout of the Wntless (Wls) gene in type I collagen (Col1a1)-expressing cells (Wls<sup>col</sup> mutants). At a young age (1 month), BM HSCs in Wls<sup>col</sup> mutants did not exhibit functional deficits, whereas these mutants exhibited an age-related BM microenvironment due to senescence of bone cells and MSCs and stimulation of osteoclast activity. These results illustrate that mesenchymal cells are more susceptible to Wnt signaling loss than hematopoietic cells. At the adult stage (4 months of age), BM HSCs in the mutants did not show any loss of function in the experimentally aged BM microenvironment. In old age (12 months of age), however, the trabecular compartment almost disappeared in the mutants and BM HSCs showed senescence-associated phenotypes, including deficits in clonogenic capacity, donor cell-derived repopulating potential, and myeloid lineage-biased differentiation, along with elevated levels of mitochondrial reactive oxygen species, senescence-associated  $\beta$ -galactosidase activity, p16INK4a protein, and phosphorylated p38 protein.

**Conclusion or Discussion:** Taken together, our findings show that Wnt signaling by Col1a1-expressing cells is indispensable for the maintenance of a normal BM microenvironment in which HSCs can exhibit functional integrity.

**Keywords:** hematopoietic stem cells, mesenchymal stem cells, BM microenvironment, Wntless, Col1a1

## LOSS OF LKB1 IMPAIRS TREG FUNCTION AND STABILITY TO AGGRAVATE GRAFT-VERSUS-HOST DISEASES AFTER BONE MARROW TRANSPLANTATION

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**Purpose or Background:** Accumulating evidence suggests that reduced number of Foxp3+ regulatory T (Treg) cells contributes to the pathogenesis of acute graft-versus-host disease (aGVHD), a major adverse effect after allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, the precise features and mechanism underlying Treg defects remain largely unknown.

**Method or Case:** A total of 46 patients after allo-HSCT were enrolled, as well as 10 age-matched healthy adults as normal controls. The ratio of Tregs in bone marrow and peripheral blood was determined by flow cytometry. A series of functional assays in vitro were performed to assess the function and stability of Tregs from patients with and without aGVHD. RNA-sequencing analysis of Tregs was performed to identify molecular determinants. The expression of Lkb1 at transcript and protein levels were measured by qPCR and NanoPro 1000 system. Tregs from the healthy donors were transduced with lentivirus to interfere with the expression of Lkb1. Meanwhile, the murine aGVHD model was established, which the Lkb1-deficient or sufficient Tregs were transplanted into. The symptoms of aGVHD were monitored, and histopathological changes were detected.

**Results or Progress:** Treg frequencies were more dramatically decreased in bone marrow compared with peripheral blood from aGVHD patients, and bone marrow Treg defects were negatively associated with hematopoietic reconstitution. Tregs from aGVHD patients exhibited multiple defects including instability of Foxp3 expression, impaired suppressor function, decreased migratory capacity, and increased apoptosis. Transcriptional profiling identified the down-regulation of Lkb1 and Lkb1-regulated genes in Tregs from aGVHD patients. Knockdown and overexpression of the Lkb1 gene could respectively decrease and increase Foxp3 expression in human Tregs. Furthermore, loss-of-function assay on an aGVHD murine model confirmed that Lkb1 deficiency could impair Tregs and aggravate disease severity.

**Conclusion or Discussion:** These findings uncover multiple defects of Tregs in human aGVHD contributed by Lkb1 down-regulation, and highlight Lkb1-related pathways as potentially therapeutic targets to mitigate aGVHD.

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**Keywords:** acute graft-versus-host disease (aGVHD), regulatory T cells (Tregs), Lkb1, bone marrow (BM), allogeneic hematopoietic stem cell transplantation (allo-HSCT)

## CLINICAL SIGNIFICANCE OF ABERRANT PROMOTER METHYLATION, MUTATION AND LOSS OF PTEN EXPRESSION IN CHRONIC MYELOID LEUKEMIA PATIENTS

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**Purpose or Background:** Chronic myeloid leukemia (CML) starts in bone marrow. The BCR-ABL1 fusion oncogene is mainly involved in the pathogenesis of the disease. It translated into the BCR-ABL oncoprotein that activates number of signal-transduction pathways which affect the growth and survival of hematopoietic cells. However, the molecular mechanisms that initiate leukemogenesis are still unclear to date. Phosphatase and tensin homolog (PTEN) is frequently deleted or inactivated in various tumors. It is down regulated by BCR-ABL in CML stem cells and its deletion is associated with acceleration of disease. However, it is unknown whether PTEN functions as a tumor suppressor in human Philadelphia chromosome-positive leukemia induced by the BCR-ABL oncogene in human.

**Method or Case:** A total one hundred and nine cases for detection of promoter methylation mutation and protein expression of PTEN gene. The methylation status was performed by methylation specific PCR. Polymerase chain reaction, single-strand conformational polymorphis followed by DNA sequencing were applied for mutations detection, while protein expression was evaluated by western blot. Clinicopathologic parameters were finally correlated with above findings.

**Results or Progress:** Marginally high percentage (61%) cases were shown positive hypermethylation, in addition 72% cases shown loss of protein expression than control samples. The novel PTEN mutations were observed in 8.3%. Further, all mutated cases shown loss of PTEN expression, while 7/9 cases shown positive promoter methylation. Moreover, out of total methylated positive samples, 79% shown loss of PTEN expression and it was significantly correlated ( $p=0.06$ ).

**Conclusion or Discussion:** We found, promoter methylation is significantly correlated with loss of PTEN expression (61% vs 72 % respectively). This shows the possibility of involvement of PTEN hypermethylation in CML development. This further suggested that PTEN expression may be plays an important role in the susceptibility of the disease progression with valuable prognostic information to aid treatment strategies.

**Keywords:** PTEN, BCR-ABL, Chronic Myeloid Leukemia, Hypermethylation, Single-strand conformation polymorphism, Mutation

## PHARMACOLOGIC INHIBITION OF JAK1/2 ATTENUATES A MURINE CUTANEOUS SCLERODERMATOUS GRAFT-VERSUS-HOST DISEASE (SCL-GVHD)

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Inhibition of the Janus-associated kinases (JAK) with ruxolitinib reduces graft-versus-host disease (GVHD) after clinical and preclinical allogeneic hematopoietic stem cell transplantation (allo-HSCT). Chronic GVHD (CGVHD) is a serious and increasingly common complication, but currently available therapies have demonstrated limited efficacy. We previously demonstrated the therapeutic effect of INCB018424 (ruxolitinib) in chronic GVHD using sclerodermatous GVHD model (ICBMT 2018;53(2):200). The clinical and pathological severity of scl-GVHD in skin was significantly attenuated in ruxolitinib-treated recipients relative to scl-GVHD controls. After ruxolitinib treatment, the frequency of CD11b+ monocyte/macrophages and CD4+ T cells was markedly decreased compared to that in scl-GVHD controls. Importantly, Regulatory CD4+Foxp3+ T cells were expanded while IFN- $\gamma$ -producing CD4+ T cells were significantly decreased in ruxolitinib treatment recipients. The frequency of donor derived-CD11b+ monocyte/macrophages was especially reduced in secondary lymphoid organs of ruxolitinib-treated recipients. In order to further investigate the role of CD11b+ monocyte/macrophages after treatment ruxolitinib in allo-HSCT model, we isolated CD11b+ cells from spleen of allogeneic recipients. Among various cytokines, MCP-1 expression was markedly reduced and the expression of TGF $\beta$  and IL-10 was increased in CD11b+ cells of ruxolitinib-treated recipients compared to scl-GVHD controls. Ruxolitinib suppressed the proliferation of macrophage cell line, RAW264.7 cells in vitro. These results demonstrate that ruxolitinib could prevent the murine scl-GVHD by direct cytotoxic effects on macrophages. Ruxolitinib might regulate MCP-1 to inhibit macrophage infiltration into the target tissue and induce TGF $\beta$  and IL-10 to generate Tregs.

**Keywords:** scl-GVHD, JAK inhibitor

## HISTONE METHYLTRANSFERASE, SETDB1 EPIGENETICALLY MODULATES THE FATE OF BLOOD CELLS BY AFFECTING HEMATOPOIETIC GENES ALONG WITH HOX GENE EXPRESSION

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**Purpose or Background:** Identity and integrity of normal cells is dependent on proper regulation of both genome and epigenome. Improper regulation of epigenetic-mechanisms leads to transcription of both tumor-suppressor genes and oncogenes. Existing literature exposed role of epigenetic regulators in hematopoiesis and tumor formation. SETDB1 is an epigenetic regulator that methylates histone-3 at lysine-9. In melanoma, colon-cancer and breast-cancer SETDB1 levels are increased. In-vivo studies using *Drosophila* expose unknown effects of SETDB1 on hematopoietic signaling and hematopoietic tumors. dSETDB1 mutants exhibit hematopoietic defects, blood tumors and show dysplasia of the hematopoietic organ.

**Method or Case:** Immunofluorescence was performed to observe different blood cells affected in SETDB1 mutants. Real-time PCR studies were performed to reveal the genes of hematopoietic signaling pathways affected in SETDB1 mutants and to determine the levels of SETDB1 transcript in JAK/STAT mutants (hop[Tum-I]-GOF). Genome wide studies (Microarray) were conducted using SETDB1 loss of function mutants to examine differences in transcripts compared to wild type animals.

**Results or Progress:** SETDB1 loss of function results in a simultaneous effect on tumour forming blood cells (lamellocytes) and crystal cells. Lamellocytes are increased with a simultaneous decrease in the crystal cells. JAK/STAT hematopoietic mutant, hop[Tum-I] show decreased expression of SETDB1 while SETDB1 mutants have increased levels of upd3 (JAK/STAT ligand). Microarray results revealed 653 genes to be down-regulated and 598 genes were up-regulated. Furthermore, it was evident from the differential expression of the HOX genes (ADB-A and ABD-B), Toll/NF-kB pathway genes, Notch and growth factors (IDGFs) that SETDB1 modulates these genes in wild type animals.

**Conclusion or Discussion:** Results obtained from this study will be instrumental in understanding how epigenetic mechanisms, orchestrated by SETDB1 affect hematopoietic signaling, HOX genes and their link to blood cancer. Further studies can be pursued to determine SETDB1 as a therapeutic target in blood cancer.

**Keywords:** SETDB1, hematopoiesis, cancer, epigenetic mechanisms, HOX, blood



## EXPERIENCE OF AUTOLOGOUS STEM CELL TRANSPLANTATION IN DHAKA MEDICAL COLLEGE HOSPITAL

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**Purpose or Background:** The journey of autologous stem cell transplantation (ASCT) was started first in Bangladesh on March 2014 at the largest and leading tertiary care government hospital of country, Dhaka Medical College Hospital(DMCH) with joint collaboration between Massachusetts General Hospital(MGH), Boston USA and DMCH. Later two more centers eg. Apollo hospitals Dhaka and Combined Military Hospital (CMH) started the transplant program by the year 2016. The purpose of this article is to describe the outcome of autologous stem cell transplanted patients for different hematological malignancies at DMCH under Department of Hematology and BMT unit.

**Method or Case:** We retrospectively analyzed 40 post auto-transplanted patients at DMCH center from March 2014 to April 2019.

**Results or Progress:** Among the total 40 patients, Multiple Myeloma (MM)=12, relapsed/refractory non-Hodgkin Lymphoma(NHL) =15, relapsed/refractory Hodgkin Lymphoma =09 and relapsed Acute Myeloid Leukemia (AML) =04. The M:F =33:7, average age 36.56 years (16-58Y) for all cases. All the myeloma patients were conditioned with high dose Inj melphalan (200 mg/m<sup>2</sup>) , lymphoma patients were with BEAM standard regimen and AML were with standard Bu-Cy. Major post-transplant complications were bacteremia(15), pneumonia (4), Clostridium difficile colitis(3), CMV cystitis (1) and PRES(1) that were treated successfully. Two year Progression Free Survival (PFS) is 70% over a median observation period of 36 months. The Cumulative incidence of relapse is 23% and transplant related mortality (TRM) in first 100 days is nil (0%).

**Conclusion or Discussion:** Establishing stem cell transplant unit was a challenge in government hospital and it was successfully done at Dhaka Medical College Hospital with the support of government. Getting experience on autologous stem cell transplant, our next approach will be launching allogeneic stem cell transplant for hematological malignancies, aplastic anaemia and thalassemia patients.

**Keywords :** ASCT, PFS, AML, NHL, TRM, PRES

PP-030

## THE ROLE OF CD11C IN ACUTE GRAFT-VERSUS-HOST DISEASE AND HEMATOPOIETIC RECONSTRUCTION

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**Purpose or Background:** Graft-versus-host disease (GVHD) is a life-threatening complication after allogeneic hematopoietic stem cell transplantation (HSCT). Host antigen presenting cells (APCs), especially dendritic cells (DCs), are instrumental in inducing GVHD by activating donor-derived T cells. As one of the  $\beta 2$  integrin family, CD11c is highly expressed on conventional DCs and typically used as a DC marker.

**Method or Case:** To investigate the relevance of CD11c in acute GVHD (aGVHD), we used CD11c knockout mice in a model of aGVHD where bone marrow cells and splenic T cells from BALB/c donors were transplanted into C57BL/6 hosts.

**Results or Progress:** Surprisingly, we observed a decreased aGVHD related mortality and weight loss in CD11c knockout mice. Moreover, CD11c knockout mice demonstrated less inflammatory cell infiltration in the target organs and decreased IFN- $\gamma$  secretion of CD4<sup>+</sup> and CD8<sup>+</sup> T cells compared with the wild type mice. Importantly, this was associated with a reduced proliferation of donor CD4<sup>+</sup> T cells in aGVHD model and mixed lymphocyte culture in vitro, which may result from the reduced expression of MHCII, CD80 and CD86 on APCs deficient of CD11c. In addition, donor bone marrow cells deficient of CD11c failed to hematopoietic reconstruction, leading to bone marrow failure and death after transplantation.

**Conclusion or Discussion:** Our results indicate a critical role of CD11c in control the T cell priming in the initiation phase of aGVHD. Besides, CD11c contribute to the myeloid cells recruit from blood stream to bone marrow niche. Therefore, targeting CD11c at appropriate time point might be an effective strategy to alleviate aGVHD.

**Keywords:** CD11c, Acute Graft-versus-host disease, Hematopoietic Reconstruction

## CYTOMEGALOVIRUS INFECTION AND DISEASE AMONG PATIENTS OF ALLOGENEIC HAEMATOPOEITIC STEM CELL TRANSPLANTATION IN HOSPITAL AMPANG: RISK FACTORS AND CLINICAL IMPACT

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**Purpose or Background:** Cytomegalovirus infection (CMV-I) remains an important complication post allogeneic haematopoietic stem cell transplantation (Allo-HSCT). Progression of CMV-I to CMV disease (CMV-D) with end organ damage is a significant source of morbidity and mortality. This study investigated the risk factors and clinical impact of CMV-I and CMV-D among Allo-HSCT patients.

**Method or Case:** This was a retrospective, single centre, case-control study. Medical records of total 250 Allo-HSCT recipients from year 2016 to 2018 were studied. Variables associated with CVM-I and CMV-D were analyzed.

**Results or Progress:** CMV-I occurred in 38.0% of all Allo-HSCT. Of it, 6.4% progressed to CMV-D. Colitis and pneumonitis were the commonest sites involved, with the incidence of 63.2% and 21.1% respectively. Present of acute graft-versus-host disease (aGVHD) [Odds ratio (OR), 2.44; 95% confidence interval (CI), 1.44 to 4.12;  $p=0.004$ ] and source of donor other than matched sibling [OR, 3.39; 95% CI, 1.49 to 7.70;  $p=0.004$ ], were associated with CMV-I. Factors which have significant association with progression from CMV-I to CMV-D were HLA-mismatched transplantation [OR, 5.85; 95% CI, 1.06 to 32.16;  $p=0.042$ ], type of donor other than matched sibling [OR, 3.35; 95% CI, 1.03 to 10.95;  $p=0.045$ ], and present of aGVHD [OR, 11.33; 95% CI, 1.43 to 90.05;  $p=0.022$ ]. Median overall survival (OS) among patients with CMV-I was not reached. There was no different in OS between patients with CVM-I and without CMV-I ( $p=0.463$ ). As for patients with CMV-D, median OS was 9.5 months. OS was significantly lower compared to those without CMV-D ( $p=0.019$ ).

**Conclusion or Discussion:** While CMV-I did not have significant impact on OS of Allo-HSCT patients, those complicated with CMV-D did show significant lower OS. Lower threshold for starting prophylactic/pre-emptive CMV treatment should be considered in HLA-mismatched transplantation, type of transplantation other than fully matched sibling, and those with aGVHD.

**Keywords:** Cytomegalovirus infection, CMV-I, CMV disease, CMV-D, allogeneic haematopoietic stem cell transplantation, , acute graft-versus-host disease, matched sibling donor, HLA-mismatched transplantation

## MALNUTRITION OF PATIENTS BEFORE ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION HAS INFLUENCE ON THE SURVIVAL AFTER TRANSPLANTATION

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**Purpose or Background:** We reported pretransplant low serum albumin were associated with shorter overall survival (OS) in patients with hematopoietic stem cell transplantation (HSCT) in the 39th Annual Meeting of the Japan Society for Hematopoietic Cell Transplantation (JSHCT2017). Since 2017 we have enhanced nutritional therapy which aims to meet the nutritional requirement of total energy expenditure. Here we reperformed a retrospective analysis.

**Method or Case:** We analyzed 125 recipients who underwent first HSCT between 2010 and 2018. The median age was 56 years (range, 16-73). The major primary disease contained AML (n=56) and MDS (n=28), and the major graft source was unrelated CB (n=52) and BM (n=42). We used serum albumin and body mass index (BMI) for assessment of nutritional status.

**Results or Progress:** A shorter OS was observed among patients with low serum albumin ( $<3.9$ , n=65) than those with normal ( $\geq 3.9$ , n=60) (median 361 days versus 1720 days,  $p=0.036$ ). In JSHCT2017, we reported patients with low serum albumin (n=16) had shorter OS than patients with normal (n=23) in non-remission cases (median 124 days versus 242days,  $p=0.0129$ ). However, OS showed no significant difference between the two groups (median 230 days, n=28 versus 526days, n=42,  $p=0.352$ ). Pretransplant BMI had no influence on OS among three BMI groups ( $BMI < 18.5$ ,  $18.5 \leq BMI < 25$ , and  $BMI \geq 25$ ) (median 526 days versus 766 days versus 877days,  $p=0.545$ ). In JSHCT2017, our multivariate analysis showed OS was significantly shorter in non-remission, low performance status, and low serum albumin group compared with the normal group ( $p=0.000$ ,  $p=0.002$ ,  $p=0.039$ ). However, this multivariate analysis showed OS was significantly shorter only in non-remission group ( $p=0.000$ ). We found tendency that low serum albumin correlate with early treatment-related mortality.

**Conclusion or Discussion:** Our experience suggests that pretransplant malnutrition is a negative factor for OS, however, sufficient nutritional therapy might reduce early mortality after HSCT.

**Keywords:** hematopoietic stem cell transplantation, nutrition

## EFFICACY AND SAFETY OF HIGH-DOSE BUDESONIDE/FORMOTEROL(320/9 mcg) IN PATIENTS WITH BRONCHIOLITIS OBLITERANS SYNDROME AFTER ALLOGENEIC HSCT

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**Introduction:** Bronchiolitis obliterans syndrome (BOS) is a rare, progressive and irreversible airway disease associated with significant mortality after allogeneic hematopoietic stem-cell transplantation (HSCT). In this study, we investigated the therapeutic effect of high dose budesonide/formoterol among patients who were diagnosed with BOS after HSCT already using low dose budesonide/formoterol.

**Methods:** Seventy-seven patients diagnosed BOS after an allogeneic HSCT who had been treated with budesonide/formoterol 160/4.5mcg bid per day and raised their dose to 320/9 mcg bid per day during the period between March 2009 and February 2019 were enrolled. Pulmonary function test and COPD assessment test (CAT) were performed before and after changing the drug dose. Efficacy was assessed within 3 months after increasing the drug dose; the primary variable was changes in forced expiratory volume in 1 second (FEV1) and CAT score. Safety was assessed as the incidence of pneumonia within 3 months after increasing the drug dose.

**Results:** After treatment of budesonide/formoterol 320/9mcg twice a day for weeks, FEV1 and FVC increased compared to measure before starting high dose treatment ( $0.04 \pm 0.26L$ ,  $p=0.182$  and  $0.03 \pm 0.42 L$ ,  $p=0.519$ , respectively). Total CAT score decreased but statistically not significant. Of all patients, 34.2% patients had a significant increase in FEV1 of more than 100 ml and 35.3% patients showed a significant decrease of greater than 2 points in CAT score. These 100 ml and CAT 2 points are the minimal clinically important difference (MCID) of FEV1 and CAT, respectively. In safety assessment, 7 patients got pneumonia within 3 months before budesonide/formoterol 320/9mcg treatment and 9 patients got pneumonia within 3 months after budesonide/formoterol 320/9mcg treatment and there was no significant difference between two groups.

**Conclusion:** Our data support the efficacy and the safety of high-dose budesonide/formoterol (320/9 mcg) treatment in patients for BOS after allogeneic HSCT.

**Keywords:** BOS, HSCT, Budesonide/formoterol

PP-034

## CLINICAL ANALYSIS OF EPSTEIN-BARR VIREMIA AND PTLD AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Purpose or Background:** Epstein-Barr virus-related post-transplant lymphoproliferative disorder (EBV-PTLD) is a rare but life-threatening complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT) in children.

**Method or Case:** We retrospectively analyzed 331 EBV DNAemia cases, studied the clinical features, outcomes and correlative prognostic factors of 12 pediatric PTLD cases in 794 consecutive allo-HSCT between April 2010 and March 2018 in Shanghai Children's Medical Center.

**Results or Progress:** The overall incidence of EBV DNAemia after allogeneic HSCT was 41.7%, varying from 23.7% in matched family donor to 44.7% in mismatched family donor, 45.7% in matched unrelated donor, and 46.2% in mismatched unrelated donor recipients. The median day to EBV DNAemia was 46 days (range, 13 to 568 days). The use of anti-thymocyte globulin ( $P < 0.001$ ,  $P < 0.05$ ), grafts with higher CD34<sup>+</sup> cell counts ( $P = 0.023$ ,  $P < 0.05$ ), III-IV grade acute GVHD ( $P = 0.006$ ,  $P < 0.05$ ) were independent risk factors for EBV infection. The mortality was 18.3% (57/310) in EBV DNAemia, 47.6% (10/21) in EBV diseases and 58.3% (7/12) in EBV-PTLD. There was no statistically significant difference in 3-year overall survival between EBV DNAemia and non-EBV DNAemia ( $P = 0.282$ ,  $P > 0.05$ ). EBV DNAemia had high survival rate than EBV diseases ( $P < 0.001$ ,  $P < 0.005$ ). A decrease in EBV DNAemia of at least 1 log<sub>10</sub> after two weeks of rituximab was significant correlated with high survival rate ( $P = 0.045$ ,  $P < 0.05$ ). Extra nodal disease or complications such as pneumonia and renal failure ( $P = 0.015$ ,  $P < 0.05$ ) and the positive EBV DNAemia within 3 weeks after the first dose of rituximab treatment ( $P = 0.015$ ,  $P < 0.05$ ) were predictors for poor prognosis.

**Conclusion or Discussion:** Anti-thymocyte globulin or total body radiotherapy, grafts with higher CD34<sup>+</sup> cell counts, III-IV grade acute GVHD are more likely to experience high-risk EBV reactivation. If EBV DNAemia progressed to EBV diseases, transplant-related mortality was significantly elevated. Extra nodal disease or complications and EBV-DNA status had a close association with the prognosis of PTLD in children.

**Keywords:** post-transplantation lymphoproliferative disorder, allogeneic hematopoietic stem cell transplantation, Epstein-Barr virus, Children

## HIGHER INCIDENCE OF HUMAN HERPES VIRUS 6 VIREMIA IN UNMANIPULATED HAPLOIDENTICAL STEM CELL TRANSPLANTATION COMPARED WITH HLA-IDENTICAL SIBLING TRANSPLANTATION IN PATIENTS WITH MALIGNANT HEMATOLOGICAL DISEASE

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**Background:** Human herpesvirus 6 (HHV-6) is relatively common after allo-HSCT. But the situation of HHV-6 post haploidentical HSCT and HLA-matched transplantation was not compared prospectively.

**Method:** We prospectively monitored HHV-6 viremia until day 100 post haplo-HSCT and HLA-matched HSCT in patients with malignant hematologic disease.

**Results:** From November 2016 to March 2017, 136 patients were included in the study. In total, 75 male patients and 61 female patients, with a median age of 25 years old (range: 2–58 years), finished the study and were enrolled in the analysis. Within 100 days post-transplantation, 27 patients (27/136, 19.9%) developed HHV-6 viremia with a median day of 14 (7–98) days. The median copies of HHV-6 was  $1.45 \times 10^3$  ( $5.48 \times 10^2$ – $2.00 \times 10^4$ ) copies/ml. The cumulative incidence of HHV-6 was  $5.9 \pm 4.0\%$  in patients with sibling donor compared with  $25.5 \pm 4.3\%$  in patients with haplo-HSCT on day 100 post HSCT. The median duration time of HHV-6 was 7 (7–21) days. In multivariate analysis, transplantation type was the only independent risk factor for the development of HHV-6 viremia and CMV viremia post-HSCT. A prior HHV-6 viremia was an independent risk factor for grade 2–4 GVHD. But HHV-6 viremia did not influence NRM and OS in the present study.

**Conclusion:** HHV-6 reactivation was statically higher in patients received haplo-HSCT than in patients received HLA-matched HSCT. Transplantation type is the only independent risk factor for the development of HHV-6 viremia.

**Keywords:** Human herpesvirus 6 (HHV-6), cytomegalovirus, acute graft-versus-host disease, hematopoietic stem cell transplantation

PP-036

## SPECTRUM OF CHRONIC LYMPHOPROLIFERATIVE DISORDERS IN PATIENTS PRESENTING WITH LYMPHOCYTOSIS

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**Purpose or Background:** Clinical presentation of chronic lymphoproliferative disorders (LPD) varies tremendously depending on the type of lymphoma. In many cases lymphocytosis with characteristic morphology is the only presenting feature. The aim of the study was to assess the spectrum of chronic LPD in patients presented with lymphocytosis.

**Method or Case:** Consecutive cases of bone marrow aspirate and trephine were analyzed from January to November 2018. Patients for whom the bone marrow was done for the evaluation of lymphocytosis were studied for the presence of LPD, sub-types, presenting symptoms and patients' characteristics. The diagnosis and classification of chronic LPD were based on criteria proposed by W.H.O Tumors of Haematopoietic and Lymphoid Tissues.

**Results or Progress:** A total of 3334 bone marrow specimens were received during study period. Out of 3334, 103(3%) patients had their bone marrow done for lymphocytosis. Of these, 102(99%) were diagnosed as chronic LPDs. Male:female ratio was 3.6:1 with median age of 60 years (21-85). Seventy percent presented with B-symptoms. The median absolute lymphocyte count was  $45 \times 10^9/L$  ( $5.3-480 \times 10^9/L$ ). One hundred (98%) patients were classified as B-cell LPD, 1% each of T-cell LPD and unclassified LPD. Chronic lymphocytic leukemia was the most common form, occurring at a frequency of 60% of all chronic LDP. Fifty eight percent presented with advanced stage disease (Rai's Stages III/IV; Binet's Stage C).

Other chronic LPDs identified in this study included mantle zone lymphoma (13%), prolymphocytic leukemia (3%), hairy cell leukemia and diffuse large B-cell lymphoma (2% each) followed by follicular lymphoma, lymphoplasmacytic lymphoma, Burkitt lymphoma and T-cell LPD (1% each).

Fifteen percent of B-cell LPDs could not be classified further. Two patients had associated autoimmune hemolytic anemia.

**Conclusion or Discussion:** Our study showed that about 99% of the patients presenting with lymphocytosis had underlying lymphoproliferative disorder of which B-cell chronic lymphocytic leukemia was found to be most common.

**Keywords:** Lymphocytosis, lymphoproliferative disorders, Chronic lymphocytic leukemia



## COMPARING BEEAM VS BEAM AS CONDITIONING REGIMEN OF HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR PATIENTS WITH LYMPHOMA - TAIWAN BONE MARROW TRANSPLANTATION REGISTRY (TBMTR) REPORT

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**Background:** High dose chemotherapy and autologous stem cell transplantation (auto-HSCT) remained the standard treatment for relapsed or high-risk lymphoma. But conditioning regimen with Bendamustine, Etoposide, Cytarabine and Melphalan (BeEAM) had rarely been compared with conventional BCNU-based regimen (BEAM).

**Methods:** In this nationwide study, we retrospectively analyzed 375 consecutive patients with lymphoma receiving BeEAM (n = 154) or BEAM (n = 221) as conditioning regimen for auto-HSCT during 2001 to 2016 from database registry.

**Results:** The median age was 52 and 53 for BeEAM or BEAM, respectively. Rituximab was added to 35% of BeEAM and 28% of BEAM group. Hodgkin lymphoma, diffuse large B cell lymphoma, mantle cell lymphoma (MCL), indolent B cell lymphoma (iNHL), and T cell lymphoma occupied 14.9%, 40.3%, 7.8%, 34.4%, and 16.9%, respectively for BeEAM group, and 16.3%, 43.4%, 9.0%, 26.7%, and 14.9%, respectively for BEAM group. There were 50.6% of BeEAM patients and 48.9% of patients in stage IV. Fifty-four percent of BeEAM patients and fifty-two percent of BEAM patients, respectively, were in complete response before auto-HSCT. Median neutrophil engraftment was 10 days for both BeEAM and BEAM group. One-month mortality was 1.3% for BeEAM group and 0.9% for BEAM group (n = 0.7). Progression free survival (PFS) was 67.7% and 62.2% at one- and two-year, respectively, for BeEAM group and 61.6% and 49.5%, respectively, for BEAM group (p = 0.63); while overall survival (OS) was 85.6% and 76.3%, respectively, for BeEAM group and 79.6% and 67.5%, respectively, for BEAM group (p = 0.24). Subgroup analysis found patients with iNHL and MCL had particularly high OS of 93.5% at 2 year in BeEAM group, comparing a 45.3% at 2 year in BEAM group (p = .03). Patients with stage IV disease also had a better OS in BeEAM than BEAM group (2 yr 90% vs 62%, p = .01).

**Conclusion:** BeEAM regimen has comparable neutrophil engraftment, one-month mortality, PFS, and OS to BEAM regimen for auto-HSCT in lymphoma patients. However, for patients with iNHL and MCL or patients with stage IV disease, BeEAM may has some OS benefit over BEAM regimen, which warrants a prospective randomized study.

**Keywords:** Autologous stem cell transplantation, lymphoma, Bendamustine, Carmustine, conditioning

PP-038

## DOWN-REGULATION OF INTRACELLULAR REACTIVE OXYGEN SPECIES ATTENUATES P-GLYCOPROTEIN-ASSOCIATED CHEMORESISTANCE IN EPSTEIN-BARR VIRUS-POSITIVE NK/T-CELL LYMPHOMA

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Epstein-Barr virus (EBV)-positive extranodal NK/T-cell lymphoma is a rare and highly aggressive disease with a poor prognosis and strong resistance to anti-cancer drugs. Reactive oxygen species (ROS) are closely related to tumorigenesis and P-glycoprotein (P-gp) is highly expressed in various cancers. However, the exact relationship between ROS and P-gp in EBV-positive lymphoma remains unclear. In this study, we demonstrated that EBV latent infection induced intracellular ROS production and increased ROS levels triggered elevated P-gp expression, which resulted in strong resistance to existing anti-cancer drugs in EBV-positive lymphoma cell lines and in patients' tissue samples. We also verified that regulation of intracellular ROS reduced P-gp expression and function via inhibition of STAT1 phosphorylation. These results indicate that treatment with a ROS scavenger is a potential therapeutic strategy to overcome resistance to anti-cancer drugs by downregulating the expression of P-gp in EBV-positive NK/T-cell lymphoma.

Keywords : Epstein-Barr virus (EBV), P-glycoprotein (P-gp), extranodal NK/T-cell lymphoma (ENKTCL), multi-drug resistance (MDR), reactive oxygen species (ROS)

## UPRONT AHSCT IN NON HODGKIN LYMPHOMA-BETTER OUTCOME?

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**Purpose or Background:** High dose therapy (HDT) followed by autologous hematopoietic stem cell transplantation (AHSCT) is recognized as a standard of care for relapsed/refractory Non-Hodgkin Lymphoma (NHL). There are many studies which have demonstrated improved disease free survival (DFS) and overall survival (OS) with AHSCT in these patients.

**Method or Case:** This is a retrospective study where patients who had undergone AHSCT from October 1997 to September 2017 in 2 hospitals in Malaysia were included. Patients' demographic data and clinical information were collected. The risk groups were categorized into 2 groups via the International Prognostic Index (IPI); whereby IPI score of 0-2 were defined as low risk and IPI score of 3-5 were considered as high risk. This study aims to determine if upfront AHSCT do improve patients' clinical outcome.

**Results or Progress:** A total of 148 patients (male: female 92:56) were included. Majority of patients had B cell lymphoma (85.1%). The median age at diagnosis was 46 (ranges from 15 – 69) years. The median period of diagnosis to AHSCT was 9.5 (range 2-112) months. Majority of patients (88.5%) were transplanted in complete remission (CR) and the remaining (11.5%) in partial remission (PR). 68% of patients were categorized as low risk and 32% patients were categorized as high risk. The transplant related mortality (TRM) was 3.4%. The overall survival (OS) and event free survival (EFS) at 3 years were 70.1% and 62.6% respectively. Patients who were transplanted in first CR had significantly better OS and EFS, p value of <0.0001. The TRM of 3.4% is similar to what was reported in other centres internationally.

**Conclusion or Discussion:** The significantly better clinical outcome of patients transplanted in first CR may suggest that upfront AHSCT is feasible and may improve outcomes. However, further studies would be required to confirm this finding.

**Keywords:** Autologous stem cell transplantation (ASCT), High-dose therapy (HDT), Non-Hodgkin lymphoma (NHL), Upfront transplant

PP-040

## JAK2 V617F MUTATION IN PATIENT PRESENTING WITH SPLANCHNIC VEIN THROMBOSIS, AMPANG HOSPITAL (MALAYSIA) EXPERIENCE

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**Background:** Splanchnic vein thrombosis is one of the typical manifestations of myeloproliferative neoplasm (MPN), commonly in Polycythemia Rubra Vera (PRV) and Essential Thrombocythemia (ET). However, establishing the diagnosis of MPN in these patients is often challenging. We set out to evaluate the frequency of JAK2 V617F mutations in patient presenting with splanchnic vein thrombosis in samples sent to the Clinical Referral Hematology Laboratory, Hospital Ampang, which is the referral laboratory for all hospitals within the Ministry of Health in Malaysia.

**Method:** We retrospectively investigated all samples sent for JAK2 V617F in year 2016 and 2017 who had splanchnic vein thrombosis which include hepatic, portal, splenic and superior mesenteric vein thrombosis that are confirmed either by Ultrasound or Computed Tomography (CT) imaging. JAK2V617F mutation analysis was done by Amplification Refractory Mutation System (ARMS) PCR.

**Results:** There were a total of 53 cases (29 men and 24 women) with history of splanchnic vein thrombosis in our database for 2016 and 2017. 13 patients (24.5%) were found to have JAK2 V617F mutation in which 6 patients had portal vein thrombosis. Of these, 5 patients had isolated thrombocytosis and 4 patients had an increase in all three cell lines (haemoglobin, platelet and white cell count), while the remaining 4 cases had normal count at the time of sampling. In subsequent follow up, we found that 5 (9.4%) patients were diagnosed with MPN. The final diagnosis for the remaining cases are not known.

**Conclusion:** Despite thrombosis being a common manifestation of MPN, the role of screening JAK2 V617F mutation in all patients presenting with splanchnic vein thrombosis without other features of MPN is unclear. However, although the prevalence of JAK V617F in this study is low, its identification appears to be useful for an accurate diagnosis and further management of MPN.

**Keywords:** JAK2V617F, Myeloproliferative Neoplasm, Splanchnic Vein Thrombosis

## APPROACH FOR DIETARY COUNSELING USING A UNIFORM DOCUMENT CREATED BY A MULTIDISCIPLINARY TEAM IN OUR HOSPITAL

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**Background:** Dietary restrictions are required for patients who undergo hematopoietic stem cell transplantation (HSCT) because of its strong myelosuppression and immunosuppression owing to conditioning regimens and immunosuppressants. Consuming appropriate foods is very important, and patients may have diverse questions, making it difficult for all nurses to provide information in a uniform manner. Therefore, we considered that it was necessary to generate a more practical and educational material based on the guideline for infection management after HSCT presented by the Japan Society for Hematopoietic Cell Transplantation.

**Methods:** A multidisciplinary team comprising long-term follow-up nurses, dietitians, and attending physicians created a practical document about food for patients who have undergone HSCT. It contains concrete examples and content that patients often ask medical staff. Moreover, it is divided into three parts according to the periods after HSCT conditioning regimen: (1) from initiation of the conditioning regimen to neutrophil engraftment, (2) from neutrophil engraftment to discharge, and (3) after discharge. We evaluated the usefulness of the document.

**Results:** Most nurses used the document in dietary counseling for patients who underwent HSCT. The opinions of the nurses who used the document were as follows: "The document meets HSCT patients' needs and interests", "It has become easier to give guidance to HSCT patients because the content is divided into three periods", and "For child patients, school meals also should be considered."

**Discussion:** The quality of dietary counseling depended on nurses' prior experiences of HSCT. However, the uniform document seemed to allow even inexperienced nurses to provide better guidance to patients with greater confidence than before. Because we created the document for adult patients, we must modify it for child patients in the future.

**Conclusion:** The document considerably created by a multidisciplinary team was helpful for both patients and medical staff.

**Keywords:** Dietary restrictions, HSCT, multidisciplinary team

## INFORMATIONAL NEEDS AND QUALITY OF LIFE OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS AND THEIR CAREGIVERS VISITING LONG-TERM FOLLOW-UP CLINICS WITHIN ONE AND HALF YEARS

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**Purpose:** To examine the relationship between fulfillment of informational needs and health-related quality of life (HRQOL) among allogeneic hematopoietic stem cell transplant (HSCT) recipients and their caregivers who visit long-term follow-up (LTFU) clinics within 1.5 years post-HSCT.

**Method:** We conducted a cross-sectional survey at two university hospitals in Japan between May and December 2018, using self-administered questionnaires and medical records. Informational need categories for patients and caregivers were created based on previous research and patient interviews, and termed General information, Treatments post-discharge, Side-effects and complications, Self-care, Psychosocial problems, and Social resources. HRQOL of patients and caregivers was measured using Functional Assessment of Cancer Therapy-Bone Marrow Transplant and Caregiver Quality of Life Index-Cancer, respectively. The pooled regression actor-partner interdependence model approach was employed to analyze the relationships, using R ver.3.6.0.

**Results:** Fourteen patient-caregiver dyads were included; the majority of patients were male (n = 12, 86%) and most caregivers were female (n = 12, 86%). Most patients were diagnosed with acute myeloid leukemia (n = 5, 36%). Eight patients (57%) received reduced-intensity conditioning. For both patients and caregivers, fulfillment of informational needs regarding Side-effects and complications (Estimates = 0.55, t(16) = 4.88, P < .001) and Self-care (Estimates = 0.73, t(13) = 5.02, P < .001) exerted actor effects on their own HRQOL, whereas fulfillment of informational needs regarding Psychosocial problems (Estimates = 0.35, t(13) = 2.90, P = .012) exerted a partner effect on the mutual HRQOL.

**Conclusion:** Multidimensional physio-psychosocial approaches towards patients and their caregivers are important to enhance their HRQOL during the acute phase post-HSCT. Detailed overviews of and methods to cope with patients' psychosocial issues should be provided before discharge, especially to caregivers unable to visit LTFU clinics.

**APBMT&ICBMT 2019**

- 24<sup>th</sup> Annual Congress of APBMT  
- 24<sup>th</sup> Annual Congress of KSBMT  
*For the best stem cell transplantation*

**Acknowledgements:** This work was supported by a grant-in-aid of "YAMAJI FUMIKO NURSING RESEARCH FUND."

**Keywords:** Dyadic data analysis, Family Caregivers, Hematology, Long-Term Care, Psycho-Oncology

PP-043

## EARLY WARNING INDICATORS FOR HEMATOPOIETIC STEM CELL TRANSPLANT-ASSOCIATED THROMBOTIC MICROANGIOPATHY

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**Purpose:** Early diagnosis of TA-TMA is difficult , It is easy to make missed and delayed diagnosis. The prognosis is extremely poor and the mortality rate is high to 60-90% when the diagnosis and treatment of TA-TMA is not in time. Early warning indicators for TA-TMA patients can apply to clinical treatment and nursing work to make early diagnosis, early treatment, minimize TA-TMA related mortality.

**Method:** A rigorous literature search strategy was applied to provide evidence-based induction of early warning indicators for TA-TMA patients. The early clinical manifestations of 7 TA-TMA patients diagnosed in our center were retrospectively analyzed. Then the preliminary early warning indicators for TA-TMA was initially built. The early warning indicator system of TA-TMA was established through the Delphi method for evidence-based nursing research and two rounds of correspondence.

**Results or Progress:** Most of patients developed to TA-TMA at +20d from +23d after transplantation. The risk factors of TA-TMA were applicating of calcineurin inhibitors, GVHD, infection, having Busulfan and sirolimus in condition, with HLA mismatch donor. The systolic blood pressure (elevated >20mmHg), urine protein (elevated >30 mg/mL), serum lactate dehydrogenase ( LDH ) level (elevated 2 times more than normal) and indirect bilirubin ( increased ) occurred at 10-14 days before making diagnosis of TA-TMA. Patients with unexplained hemoglobin and thrombocytopenia after successful engraftment are highly warn to be developing to TA-TMA.

**Conclusion:** Nurses should identify high-risk patients for the early identification of TA-TMA. The indicators of high-risk patients should be monitored follows: Blood, observing the presence of newly developed thrombocytopenia or anemia during recovery of blood corpuscle ; Blood pressure, LDH, renal function index ; Heart rhythm, heart rate, blood oxygen saturation, early ultrasonic cardiogram when needed ; Consciousness state, muscle tension, orientation ability, be cautious to indication of epilepsy such as dizziness and limb numbness ; Whether have abdominal pain or fecal occult blood.

**Keywords:** Early warning indicators, hematopoietic stem cell transplant-associated thrombotic microangiopathy



## NURSING MANAGEMENT FOR SUCCESSFUL PERIPHERAL BLOOD STEM CELL COLLECTION: A SINGLE CENTER REPORT OF 145 CASES

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**Purpose:** To assess the function and significance of nursing methods in peripheral blood stem cell (PBSC) collection.

**Method:** A total of 198 PBSC collection from 145 G-CSF mobilized donors (142 allogeneic cases, 1 syngeneic cases and 2 autologous cases) were performed by using Auto PBSC program by COBE Spectra 6.1 blood cell separator between July 2017 and April 2019. The ratio of men to women is 88:57. The median age is 36 (range:1 to 69 years). Donors with less than 20kg were given erythrocyte prefilling pipeline and those with poor vascular conditions were given femoral vein catheterization. Before collection, psychological nursing and explanation of the collection principle, safety measurement and dietary requirements should be done. During the collection, continuous vital signs monitoring is given. Nursing staff deal with the alarm timely to avoid panic, observe color change of the enriched grafts and make necessary adjustment. In addition, nursing staff need to observe carefully any adverse effect and supply calcium gluconate, reduce the collecting speed if the donor felt uncomfortable and inform doctor. Health education should also be carried out after collection, such as eating a high-protein, high-calcium diet, drinking more water and having a good rest.

**Results:** Among 145 donors, 95 cases were collected once, 47 for twice and 3 for three times. Sufficient mononuclear cells and CD34+ cells were collected in all cases. Apheresis process of PBSC was smooth and the vital signs of donors were all stable. Ten of the donors had mild hypocalcemia with symptomatic relief after oral calcium. No severe adverse effect occurred during PBSC collection.

**Conclusion:** Our PBSC collection results have shown that good nursing including psychological counseling before collection, skilled apheresis techniques, monitoring for adverse reaction play an important role in harvesting sufficient enriched grafts and improving the comfort and satisfaction of donors.

**Keywords:** Donor, PBSC Collection, Nursing

## IMPROVE THE FATIGUE SYMPTOMS IN ELDERLY PATIENT UNDERWENT HAPLOIDENTICAL STEM CELL TRANSPLANTATION – A NURSING EXPERIENCE

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**Background:** Nearly five-hundred patients in Taiwan underwent stem cell transplantation every year. From year 2009 to 2018, 14% of these patients are over age of 60. The probability of elderly patients who feel fatigue after receiving the chemotherapy could be as high as 70%. The elderly patients also have a much higher chance of developing complications, and they may feel upset and helpless. Here we share a case of elderly patient, whose fatigue symptoms had been successfully improved by multiple nursing strategies.

**Case:** Patient is a 66-year-old female with acute lymphocytic leukemia who underwent the haploidentical allogeneic stem cell transplantation (allo-SCT) in National Taiwan University Hospital. The patients' fatigue level during the nursing period was assessed constantly by a fatigue score with scale of 0-10. The patient's initial self-assessed fatigue index is 9. She was reluctant to get off of bed and asked to toilet and having rub-bath in the bed, suggesting the patient had not adjusted well and the patient's daily life was seriously affected.

**Progress:** The patient was encouraged to do simple physical movements at the bedside. The physical activity time is decided by the patient, and the frequency and duration of physical activity would be increased according to the patient's feeling of fatigue. Light music was played before bedtime or the earplug is used to avoid noise so that the patient can have a good night sleep. After the preceding nursing measures, the patient could get out of bed up to 5 times a day, and about 10 minutes each time; the patient fatigue index decreased down to 1 about twenty days after the nursing intervention.

**Discussion:** In comparison with younger patients, the elderly patients have more difficulty making the adjustment during allo-SCT. On the basis of the individual situation and self-care ability, the nursing plans should be proposed to provide a simple and specific guidance, and to fulfill the patient's feeling of autonomy and thus the patient will be more willing to participate in medical decision-making, which would be part of key factors to a successful and high-quality allo-SCT.

**Keywords:** acute lymphocytic leukemia, stem cell transplantation, elderly, fatigue, autonomy

## HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN WITH APLASTIC ANEMIA

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**Background:** Several studies showed that efficacy and safety of haplo-identical stem cell transplantation from a related mismatched donor (haplo-SCT) for aplastic anemia (AA). However, an optimal conditioning regimen is unclear in haplo-SCT.

**Methods:** We retrospectively analyzed the outcome of 43 Japanese children (<16 years old) with acquired AA who received haplo-SCT between 1992 and 2013. The data management committee of Japan Society for Hematopoietic Cell Transplantation (JSHCT) approved this study.

**Results:** The median age at the time of haplo-SCT was 10 years (range, 1-15 years). The median interval between diagnosis of AA and haplo-SCT was 292 days (range, 20-3417 days). Graft sources included 4/6 HLA matched (n = 26) and 3/6 HLA matched (n = 17) haploidentical bone marrow and/or peripheral blood. The conditioning regimens varied according to individual institutes. Twenty patients received fludarabine (FLU) + cyclophosphamide (CY)/Melphalan (MEL) + antithymocyte globulin (ATG) ± total body irradiation (TBI). Thirteen received CY+ ATG. The remaining 10 received other various conditioning regimens. As for GVHD prophylaxis, cyclosporine (n = 20) or tacrolimus (n = 23) based regimens were used. Primary graft failure (GF) was observed in five patients. Seven patients experienced secondary GF, and thus sustained engraftment was observed in 31 patients. The 5-year overall survival (OS) and failure-free survival (FFS) of all patients were 76% (95% CI, 60%–86%) and 62% (95% CI, 46%–75%), respectively. Grade II–IV acute GVHD was observed in 10 patients. Eleven patients developed chronic GVHD. The 5-year OS of the 20 patients who received FLU + CY/MEL + ATG ± TBI was tended to be better than those of the 23 patients who were conditioned with other regimens (90% vs. 65%; P = 0.076).

**Conclusion:** Our study suggests that FLU+CY/MEL+ ATG ± TBI is potentially an optimal conditioning regimen for haplo-SCT in children with AA.

**Keywords:** aplastic anemia, child, haplo, conditioning

## BETTER FAILURE-FREE SURVIVAL (FFS) AND GRAFT-VERSUS-HOST DISEASE-FREE/RELAPSE FREE SURVIVAL (GRFS) WITH FLUDARABINE-BASED CONDITIONING IN STEM CELL TRANSPLANTATION (SCT) FOR APLASTIC ANEMIA (AA) IN CHILDREN

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**Purpose:** This study was aimed to assess the outcome of SCT, including overall survival (OS), FFS and graft-versus-host disease (GvHD)-free/relapse-free survival (GRFS), and to analyze prognostic factors in children with AA.

**Materials and Methods:** Among 161 pediatric AA cases from 1991 to 2008, 43 allogeneic SCT recipients were enrolled to investigate the demographic characteristics, survival outcomes and prognostic factors.

**Results:** With the median follow-up of 8.2 years, the 10-year K-M estimated OS, FFS, GRFS were 86.0%, 60.5%, and 51.2% respectively. Matched sibling donors (MSD, n=28) showed better 10-yr OS than unrelated donors (UD, n=15) (96.4% vs. 66.7%; P=0.006). Engraftment failure was seen in 13 patients (30.2%). Donor-type aplasia was seen in 13.8% (4/29) after Flu-based conditioning (Flu-group), while in 42.6% (6/14) after cyclophosphamide (Cy)-based regimen (Cy-group) (P=0.035). Six patients died. The 10-year OS in Cy-group was 92.9% (n=14, all MSD), while that of Flu-group was 82.1% (n=29; P=0.367). But Flu-group tended to have better FFS and GRFS than Cy-group, although Flu-group had less MSDs (41.4% vs. 100%; P=0.019), and higher proportion of previous immunosuppressive treatment (IST; 62% vs. 21.4%, P=0.012). In MSD transplants, OS was similar between Flu-group (100%, n=14) and Cy-group (92.9%, n=14), while FFS (100.0% vs. 42.9%; P=0.001) and GRFS (85.7% vs. 35.7%; P=0.006) were significantly better in Flu-group. Stem cell sources, irradiation in the conditioning, method of GVHD prophylaxis did not significantly influence the outcome. The independent predictors of OS were UD transplants (OR=10.975, P=0.029), and viral reactivation (OR=6.494, P=0.037).

**Conclusion:** This study reviewed SCT outcomes for pediatric AA with changes of transplant strategies over last 25 years. The FFS and GRFS was higher in Flu-group than in Cy-group, especially in sibling transplantation. Graft failure including donor-type aplasia remains troublesome even with Flu-based conditioning. Further refinement of transplant strategies to ensure better quality-of-life should be pursued.

**Keywords:** Aplastic anemia, Children, Fludarabine, Survival

## HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS PERIPHERAL STEM CELL TRANSPLANTATION FOR TREATMENT OF RELAPSED AND REFRACTORY WILMS TUMOR: A KPHOG RETROSPECTIVE ANALYSIS

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**Background:** Wilms tumor (WT) is the most common childhood malignant renal tumor and the survival rate has improved to almost 90%. However, the outcomes for relapsed or refractory WT have remained disappointing. High-dose chemotherapy (HDT) followed by autologous peripheral hematopoietic stem cell transplant (aPBSCT) is often utilized as a second-line treatment in relapsed or refractory WT reporting values ranging from overall survival (OS) 48% to 73%, and disease free survival 34% to 63.6%.

**Method:** We retrospectively analyzed the outcomes of WT patients with relapsed or refractory disease who received HDT followed by aPBSCT between January 2001 and December 2015 in five pediatric transplantation centers in Korea.

**Results:** Total 20 patients (11 males and 9 females) underwent HDT and aPBSCT during study period. Seventeen relapsed and three refractory diseases were enrolled. The median age of diagnosis was 3 years 5 months (range 6 month-16 years 2 months). The median time from diagnosis to transplantation was 1 year 5 months (range 9 months - 7 years 3 months). The most common conditioning regimen was Melphalan, Etoposide and Carboplatin. Four patients received tandem transplantation with Cyclophosphamide Etoposide and Carboplatin followed by Thiotepa and Melphalan. Three patients died, two with disease progression and one with treatment related toxicity. Seventeen patients are alive without disease for median 8 years (range 2 years 5 months - 13 years 5 months). The 5-year estimates for event-free survival (EFS) and OS were 85% and 90%, respectively.

**Conclusions:** These outcomes suggest HDT followed by aPBSCT for relapsed or refractory WT is well tolerated and effective strategy. Long-term follow-up is required in large patient groups to assess long-term efficacy and toxicity.

**Keywords:** Wilms tumor, Relapsed, Refractory, High dose chemotherapy, Autologous peripheral blood stem cell transplantation

## COMPARISON OF HAPLOIDENTICAL VS UNRELATED DONOR TRANSPLANTATION FOR ADULT PATIENTS WITH SEVERE APLASTIC ANEMIA

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**Purpose or Background:** This study retrospectively compared outcomes of allogeneic hematopoietic cell transplantation (SCT) from a haploidentical related donor (HAPLO) with those of well-matched (8/8) unrelated donor (WM-URD) and mismatched unrelated donor (MM-URD) in patients with severe aplastic anemia (SAA).

**Method or Case:** Total 147 adult patients with SAA who had undergone their first SCT between October 2003 and April 2018 were included: 46 of HAPLO; 67 of WM-URD; and 34 of MM-URD.

**Results or Progress:** The median follow-up was 50.2 (range, 0.2-174.1) months. Except one patient who presented a platelet engraftment failure in HAPLO, all patients achieved neutrophil and platelet engraftments with median 12 and 14 days for HAPLO, 11 and 15 days for WM-URD, and 13 and 16.5 days for MM-URD, respectively. The four-years overall survival (OS), graft failure-free survival (FFS), and cumulative incidences (CIs) of graft-failure and transplant-related mortality were similar among three groups: 89.4%, 84.3%, 6.6%, and 9.1% for HAPLO; 85.3%, 86.4%, 3.0%, and 10.6% for WM-URD; 86.5%, 85.3%, 0.0%, and 14.7% for MM-URD. The 180-days CI of grade II-IV acute graft-versus-host disease (GVHD) and moderate to severe chronic GVHD were significantly higher in WM-URD than those in HAPLO: 52.9% vs. 30.4% ( $p=0.032$ ); 36.7% vs. 11.8% ( $p=0.024$ ). But, multivariate analysis shows that type of donor was neither associated with day-180 grade II-IV acute GVHD nor moderate to severe chronic GVHD. Administration of ATG is the only factor affecting both grade II-IV acute GVHD (Hazard ratio, 0.487,  $p$ -value=0.006) and moderate to severe chronic GVHD (Hazard ratio, 0.378,  $p$ -value=0.003) in multivariate analysis.

**Conclusion or Discussion:** This study shows that there was no significant differences of major outcomes of SCT between HAPLO with WM-URD or MM-URD. In the absence of suitable matched sibling donor, host/donor features and urgency of transplant should drive us towards the best choice between these alternative donor sources for SAA patients treated with SCT.

**Keywords:** transplantation, severe aplastic anemia, unrelated, haploidentical

## REDUCED-INTENSITY HEMATOPOIETIC CELL TRANSPLANTATION FOR PRIMARY IMMUNODEFICIENCY DISORDERS: A SINGLE CENTER EXPERIENCE

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**Background:** There are many types of primary immunodeficiency disorders (PIDs), and allogeneic hematopoietic cell transplantation (HCT) is the only curative therapy for certain subtypes. Compared with conventional myeloablative conditioning, reduced-intensity conditioning (RIC) is expected to have the potential to reduce early and late complications associated with HCT. We report our single-center experience of RIC-HCT for PIDs.

**Methods:** We retrospectively reviewed 25 patients with PIDs who received RIC-HCT from 2002 to 2018 at our institute.

**Results:** Twenty-nine HCTs were performed including 4 2nd-HCT. The median age at HCT was 2 years (range 0-23). Twenty patients were male and 5 were female. The diseases of patients consisted of familial hemophagocytic lymphohistiocytosis (n=6), severe combined immunodeficiency (n=4), Wiskott-Aldrich syndrome (n=4), X-linked lymphoproliferative syndrome (n=3) and others. Two autoinflammatory diseases were included. Donor sources were CB (n=17), matched sibling BM (n=2), unrelated BM (n=3) and haploidentical BM/PBSC (n=7, CD34 selected:2, T-cell depleted:1). Conditioning regimens were mostly fludarabine + cyclophosphamide based (n=13) or fludarabine + melphalan based (n=11). Total body irradiation  $\leq 6$ Gy or thoraco-abdominal irradiation were combined in 14 cases. Anti-thymocyte globulin was used in most patients. Graft failure occurred in 5 patients, and their donor source was CB only. Four of 5 patients underwent 2nd-HCT and 3 patients were finally engrafted. The median follow-up period was 13 years (range 1-16). Ten patients (40%) died, and the cause of death in 6 of them was transplant related morbidity. Acute GVHD occurred in 14 patients (Grade I :2, II :9, III :3), and chronic GVHD was observed in 2 patients. Complete chimerism was achieved in 12 patients of 15 survivors (80%).

**Discussion:** RIC-HCT seems to be feasible for many PIDs. CBT have a high risk of graft failure comparing to other sources, so the optimal conditioning should be established in CBT.

**Keywords :** Primary immunodeficiency disorders, allogeneic hematopoietic cell transplantation, reduced-intensity conditioning

PP-051

## PLASMABLASTIC LYMPHOMA AND PLASMABLASTIC MYELOMA; IS THE TWO AN OUTCOME OF SINGLE DISEASE PROCESS?

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**Purpose or Background:** Plasmablastic lymphoma (PL) is an aggressive mature B- cell neoplasm. It shows diffuse proliferation of large (CD20 negative) cells resembling immunoblasts or plasmablasts. It occurs primarily at extra nodal sites in immunodeficiency. Plasmablastic Myeloma (PM) is a subset of myeloma with  $\geq$  2% of plasmablasts in bone marrow.

**Method or Case:** Retrieval of the case from hospital achieves.

**Clinical History:** A thirty one year old otherwise immunocompetent male presented with rapidly growing mass in right side of oral cavity for one month. Clinical examination showed ulceroproliferative growth covering 40% of oral cavity with cervical lymphadenopathy. Mass lesion was seen in right maxilla on CECT. Skeletal survey was normal. There was no B-symptom. Viral markers were negative. Serum electrophoresis (SEP) showed no M-band. FNAC showed large atypical cells with LCA (CD45) + & HMB 45- (excludes malignant melanoma) suggestive of NHL. Biopsy showed malignant cells positive for CD79a, CD138 and MUM1 & negative for CD20, CD3, CD56, CK & HMB45; suggestive of Plasmablastic lymphoma. Peripheral blood smear was normal. Bone marrow (BM) studies (aspirate & biopsy) showed 50% Plasma cells predominantly plasmablasts. After six cycles of CHOP regimen, repeat BMA showed 20% plasma cells (plasmablasts). SEP showed no M-band. Now raised values of Serum free light chain ratio (kappa/lambda)  $429/15.84=27.09$  (0.26 to 1.65), serum Beta 2 microglobulin 3.263 (1.21-2.70 mcg/mL) & serum creatinine 1.8 mg/dl were noted.

**Results or Progress:** Finally Plasmablastic myeloma was considered. After 4 cycles of thalidomide + dexamethasone, therapeutic plan was switched to Bortezomib + dexamethasone. Symptomatic improvement was seen with normal hemogram/biochemistry.

**Conclusion or Discussion:** This kind of presentation raised a question, "Can PL progress to PM? Is the two diseases outcome of single disease process?" As they share cytomorphologic and immunophenotypic features, making a precise diagnosis difficult, where as therapy and clinical presentations stand different.

**Keywords:** Plasmablastic lymphoma, Plasmablastic myeloma, Immunocompetant



## ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR MULTIPLE MYELOMA POST-AUTOLOGOUS TRANSPLANTATION

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**Background:** Salvage use of allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative option for patients with refractory or relapsed multiple myeloma (MM). However, treatment-related mortality (TRM) is high. Therefore, we investigated the risk of mortality in MM allo-HSCT recipients.

**Methods:** We enrolled MM patients receiving two HSCTs at Taipei Veterans General Hospital in Taiwan between January 2002 and October 2018. Patients without bone marrow studies and receiving allo-HSCT as the frontline therapy were excluded. The patients receiving second allo-HSCT and autologous HSCT (auto-HSCT) were served as the study and comparison groups, respectively. The primary endpoint was TRM, defined as death within 100 days after second HSCT and the second endpoint was overall survival (OS). The risk factors for mortality were identified using Cox proportional hazards models.

**Results:** We reviewed 801 MM patients. Of them, 145 patients received first auto-HSCT, of which 30 (20.7%) have received second HSCT, including 16 allogeneic and 14 autologous HSCTs. The median age at second HSCT was 53 years (range 24–66). The TRM was 43.8% and 0.0% for those receiving second allo-HSCT and auto-HSCT, respectively. The median OS from second HSCT were 0.5 (95% CI 0.2–3.1) and 2.7 (95% CI 1.7–6.0) years for allo-HSCT and auto-HSCT, respectively. In the univariate analysis, serum creatinine  $\geq 1.5$  mg/dl (HR 2.29, 95% CI 0.97–5.40) and LDH  $\geq 250$  U/L (HR 7.43 95% CI 2.19–37.00) were associated with mortality. After adjusting for serum creatinine and LDH, there were no statistically significant differences between the auto-allo-HSCT and the auto-auto-HSCT strategies. (adjusted HR 1.36, 95% CI 0.52–3.56).

**Conclusion:** The study revealed high TRM for second allo-HSCT in MM patients. Although the use of allogeneic HSCT as second HSCT might benefit from the potentially curative effect of graft-versus-myeloma effect. Physicians should be cautious and select good candidates for second allo-HSCT.

**Keywords:** allogeneic hematopoietic stem cell transplantation, autologous hematopoietic stem cell transplantation, multiple myeloma, salvage therapy, treatment-related mortality

## AUTOLOGOUS STEM CELL TRANSPLANTATION IN ELDERLY PATIENTS WITH MULTIPLE MYELOMA IN KOREA: THE KMM1807 STUDY

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**Background:** Autologous stem cell transplantation (ASCT) with high-dose chemotherapy has been established as a standard care for relatively young and fit patients with newly diagnosed multiple myeloma. On the contrary, ASCT has not been frequently performed for older group due to lack of data and limitation of national health insurance system in Korea. In this study, we assessed the efficacy and safety of ASCT in elderly patients.

**Method:** Medical records of 139 patients of 11 institutions who were diagnosed with multiple myeloma and received ASCT at age over 64 were analyzed retrospectively. Response status of pre- and post-ASCT were compared. Survival outcomes including overall survival (OS) and progression-free survival (PFS) were analyzed using Kaplan-Meier method. Safety issues were also assessed.

**Results:** Median time from diagnosis to ASCT was 6.4 months. About a quarter (26.1%) of cases were categorized as stage 3 by revised international staging system (R-ISS), and almost a half (45.3%) of patients were stratified as cytogenetically high risk. The rate of complete response (CR) including stringent CR (sCR) increased from 32 (23.0%) to 95 (68.4%) after ASCT. Overall response (sCR, CR and VGPR) rose from 85 (61.1%) to 115 (82.8%) alike. With median follow up of 35 months after ASCT, 3-year and 5-year OS were 75.9% and 58.8%, respectively. The analysis of PFS revealed 38.2% and 20.5% after 3 and 5 years apiece. Febrile neutropenia occurred in 41.9%, and nausea (76.0%), stomatitis (65.6%) and diarrhea (57.9%) were common non-hematologic adverse events in ASCT. Of all 43 deaths during follow up, disease progression (23) was the

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most common cause of mortality followed by infections in 12 patients.

**Conclusion:** In conclusion, ASCT is an effective and safe option for elderly patients with multiple myeloma to improve response and survival outcomes.

**Acknowledgement:** This study was performed as an interim analysis.

**Keywords:** myeloma, autologous, transplantation, elderly

## IMPACT OF PRE-TRANSPLANT AND POST-TRANSPLANT RESPONSES ON OUTCOMES AND SURVIVAL IN MULTIPLE MYELOMA

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**Purpose or Background:** High dose chemotherapy with autologous hematopoietic stem cell transplantation (ASCT) has been shown to improve both overall and disease free survival for patients with multiple myeloma (MM). However, the optimal timing and depth of response pre-transplant after initial induction therapy is debatable

**Method or Case:** To analyse the association of pre-and post-transplant disease response with outcomes and survival in patients with multiple myeloma. In this retrospective study, data of patients with multiple myeloma who had undergone autologous stem cell transplantation (ASCT) from 1/1/2003 to 31/12/2018 was analysed (minimum follow-up:90days). 166 patients who received an ASCT over a period of 15 years were evaluated.

**Results or Progress:** Median age of entire cohort was 55 (Range:23-68) years with male:female ratio 1.72:1. Median follow-up for the entire group was 46 (95% C.I. 41.7 – 50.3) months. Median number of cycles prior to transplant were 4 (1-26). Baseline ISS data was available in 120 patients – 34.16%(n=41) in ISS-1, 35.8%(n=43) in ISS-2 and 30%(n=36) in ISS-3. Patients were analysed in two groups – PR (partial response) and CR/VGPR (Complete response/Very good partial response). For patients in pre-transplant PR versus CR/VGPR, 4-year PFS was 20±7% and 40±7% (p=0.22), 4-year OS was 81±6% and 86±5% (p=0.41) respectively. For patients in post-transplant PR versus CR/VGPR, 4-year PFS was 13±10% and 36±6% (p=0.002), 4-year OS was 52±15% and 88±4% (p=0.003), respectively. 4-year OS and PFS for the entire cohort was 82±4% and 33±5% respectively. Amongst all 72 patients with pre-transplant PR, those who achieved post-transplant PR was 15.2%(n=11), while remaining patients achieved CR/VGPR. On univariate analysis, achievement of post-transplant CR/VGPR was an independent predictor of PFS and OS.

**Conclusion or Discussion:** Patients with pre-transplant PR have similar time to progression and overall survival, and achieving a deeper response prior to transplant is not essential.

**Keywords:** Multiple Myeloma, autologous transplant, partial response, response, survival

## DARATUMUMAB AS A BRIDGING THERAPY FOR REFRACTORY MULTIPLE MYELOMA : A CASE REPORT

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**Background:** Introduction of novel therapy as standard induction therapy in combination with autologous haematopoietic stem cell transplant (ASCT) has resulted in prolonged survival but multiple myeloma (MM) remained a chronic, incurable disease. However, the management of refractory MM remains challenging. Here we report 2 cases of refractory MM who received Daratumumab as a bridging therapy before ASCT.

**Case presentation:** 2 patients with newly diagnosed MM received Bortezomib-based regimen as induction treatment in combination with Dexamethasone and Thalidomide. However, they had refractory disease. Salvage chemotherapy was initiated but the disease progress further. These patients were later given Daratumumab in combination with Lenalidomide and Dexamethasone (DRD) as third line treatment. Due to cost limitation, they were only given 2 cycles of DRD and resulted in partial response. Subsequently, they underwent ASCT despite the short course of this therapy.

**Discussion/Conclusion:** The goal of treatment in MM is to achieve prolonged disease control with acceptable toxicity thus improved quality of life. Despite the introduction of novel therapies, ASCT remains an important component of therapy for transplant eligible patients as shown by many recent studies. The choice of effective induction regimens followed by ASCT is a very critical decision as it may lead to a deep response. In Pollux trial, the addition of Daratumumab to Lenalidomide and Dexamethasone produced a synergistic effect where it significantly lengthened progression free survival among patient with refractory disease. In Malaysia, the access to Daratumumab is limited. Although short courses were given, our patients benefit from this regimen, which acts as bridging therapy to transplant.

**Keywords:** Refractory multiple myeloma, Daratumumab, Autologous stem cell transplant

PP-056

## HYPERMETHYLATION OF TUMOR SUPPRESSOR GENES AND ITS CORRELATION WITH THE CLINICAL PROFILE OF INDIAN PATIENTS WITH MYELOYDYSPLASTIC SYNDROMES

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**Purpose or Background:** Accurate diagnosis of MDS is difficult, and its classification requires evaluation of cytopenias, bone marrow morphology, blast percentage, and cytogenetics. These factors, as well as patient performance status and red blood cell transfusion dependence, can be used to predict prognosis in MDS. IPSS scoring system has been widely used for the risk stratification of MDS patients. We have compared the molecular and clinical parameters of patients within low, intermediate and high risk groups and analysed the association in these groups.

**Method or Case:** PCR and RT-PCR was used for the mutation detection. MSP- PCR was used to assess the methylation status of tumor suppressor genes in 51 MDS patients.

**Results or Progress:** Of the 51 patients (median age 49.0 years range: 9-84years, M:F::1:1.5), 7 (14%) were high risk of which 4 transformed to leukemia. Of these 7 cases, six patients were transfusion dependent. 2 patients were positive for RAS mutations and 3 were positive for JAK2 mutation. IDH2, hTERT and FLT3 mutations were not present at all. Hypermethylation of SOCS-1 was present in 7, FHIT in 2 cases, for CALCA in 7 and for P15 in 3 cases. Out of 19 (37%) intermediate risk patients 4 transformed to acute leukemia. hTERT mutation was present in and RAS in 2 patients. 16 patients were transfusion dependent. Gene hypermethylation for SOCS-1 was present in 14, for FHIT in 11, for CALCA in 16 and for P15 in 10. Of 25(49%) low risk cases one transformed to leukemia and 21 patients were transfusion dependent. hTERT mutation was present in 3 patients. Gene hypermethylation for SOCS-1 was present in 7, for FHIT in 15, for CALCA in 8 and for P15 in 8.

**Conclusion or Discussion:** Molecular mutations and gene methylation differentially present in different IPSS risk groups. Molecular factors along with other risk factors might enhance the power of risk assessment of the MDS patients.

**Keywords:** Myelodysplastic Syndromes, India, Cytogenetics, Methylation, Tumor suppressor genes

## POOLED SAFETY ANALYSIS OF DEFIBROTIDE TREATMENT IN PATIENTS WITH HEPATIC VENO-OCCLUSIVE DISEASE/SINUSOIDAL OBSTRUCTION SYNDROME (VOD/SOS) AFTER HAEMATOPOIETIC CELL TRANSPLANTATION (HCT)

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**Background:** Defibrotide is approved for patients aged >1 month with severe hepatic VOD/SOS post-HCT in the EU, and for adult and paediatric patients with hepatic VOD/SOS with renal or pulmonary dysfunction post-HCT in the US and Canada. Safety results from patients with VOD/SOS who received defibrotide 25 mg/kg/day are summarised.

**Methods:** Data were pooled from patients with VOD/SOS and multi-organ dysfunction (MOD) post-HCT treated with defibrotide in phase 2 (NCT00003966; n=74 receiving 25 mg/kg/day) and phase 3 (NCT00358501; n=102) studies. Historical controls (HCs) from the phase 3 study (n=32) are provided for context, but not as a formal comparison. Because the expanded-access study (T-IND; NCT00628498; n=1,000) included patients with or without MOD, data from this study are reported separately.

**Results:** Median ages at HCT were 24.0, 18.0, and 14.0 years for the phase 2/3 studies, HCs, and T-IND, respectively. In phase 2/3 studies, 169/176 (96%) patients experienced treatment-emergent adverse events (TEAEs), most commonly (>10%) hypotension (37%), diarrhoea (24%), and multi-organ failure (22%). All HCs experienced TEAEs, most commonly (>30%) hypotension (50%), tachycardia (44%), diarrhoea (38%), and nausea (31%). In phase 2/3 studies, treatment-related AEs (TRAEs) occurred in 58/176 (33%) patients; any haemorrhage occurred in 101/176 (57%) patients, most commonly (>10%) epistaxis (14%). Any haemorrhage occurred in 24/32 (75%) HCs, most commonly (>10%) petechiae (28%), haematuria (16%), epistaxis (16%), pulmonary alveolar haemorrhage (16%), and lip haemorrhage (13%). In T-IND, 385/512 (75%) patients with MOD and 324/488 (66%) patients without MOD experienced TEAEs. TRAEs occurred in 118/512 (23%) patients with MOD and 92/488 (19%) patients without MOD. Any haemorrhage occurred in 166/512 (32%) and 124/488 (25%) patients with and without MOD, respectively.

**Conclusions:** The defibrotide safety profile was as expected in these critically ill patients and consistent with previous studies. In T-IND, patients with MOD experienced more AEs than those without MOD.

**Keywords:** veno-occlusive disease (VOD), sinusoidal obstruction syndrome (SOS), defibrotide, safety, adverse events, haematopoietic cell transplantation



## ALLOGENEIC STEM CELL TRANSPLANTATION FOR MDS AND MDS-RELATED MYELOID NEOPLASMS PATIENTS WITH AUTOIMMUNE / AUTOINFLAMMATORY DISEASES

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**Purpose:** Myelodysplastic syndrome (MDS) are frequently complicated by autoimmune / autoinflammatory diseases (ADs), such as Behcet's disease and MDS-associated pyrexia, which could increase the risk of transplant-related complications post allogeneic stem cell transplantations (allo-SCT). We aimed to clarify the impact of ADs on outcomes after transplantations for MDS in a single institution by retrospective analysis.

**Method:** We included MDS patients who received allo-SCT in Kyoto University hospital between 2005 and 2018. Patients with AML with myelodysplasia-related changes were also included. Primary endpoint was the impact of ADs on non-relapse mortality (NRM), and secondary endpoints were its impact on overall survival (OS), relapse, and grades II-IV and III-IV acute GVHD.

**Results:** Ninety-seven patients were included in the analysis. A total of 54 patients had MDS, 35 MDS/AML, 3 MDS/myeloproliferative neoplasm, 1 chronic myelomonocytic leukemia, and 4 AML (M6). Seventeen patients (17.5%) had ADs. Median age of patients was 49 (range, 17-68). Cumulative incidence of NRM at 5 years was higher in patients with ADs (36.6% vs 15.7%,  $p=0.0558$ ). Multivariate analysis showed that ADs were marginally associated with the risk of NRM (HR 2.46,  $P=0.087$ ). There was no significant difference in OS and relapse rate; five-year OS rates in patients with and without ADs were 51.8% (95% CI, 26.2-72.4%) and 58.5% (46.1-68.9%) ( $P = 0.456$ ); five-year relapse rate were 17.6% (4.0-39.1%) and 30% (20.1-40.5%) ( $P = 0.25$ ), respectively. Presence of ADs was marginally associated with the increased risk of grades II-IV acute GVHD (HR 1.951,  $P=0.070$ ). There were no significant differences regarding grades III-IV acute GVHD.

**Conclusion:** ADs may increase risk of NRM and mild acute GVHD for patients with MDS. Larger cohort is necessary to reassess the impact of autoimmune disease and to identify the modifiable factors that could reduce the NRM risk after transplantation.

**Keywords:** MDS, autoimmune, autoinflammatory

## OUTCOME OF HEMATOPOIETIC STEM CELL TRANSPLANT FOR SEVERE APLASTIC ANEMIA IN PAKISTAN: DATA FROM A DEVELOPING COUNTRY

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**Background:** In Pakistan, approximately 400-500 new cases of aplastic anemia are diagnosed every year and variant environmental exposures are accredited as etiological factor. Only 20-25% of patients receive stem cell transplant due to limited health resources. To determine the overall survival, risk factors for relapse and non-relapse mortality after matched-sibling donor transplant for severe aplastic anemia.

**Method:** It was a non-interventional prospective study, conducted at National Institute of Blood Disease and Bone marrow transplantation from 2011 to 2017. Severe aplastic anemia was diagnosed according to Camitta classification. Conditioning regimens used were Fludarabine/Cyclophosphamide or Fludarabine/Anti-Thymocyte Globulin (ATG). The patients were closely followed for engraftment, primary or secondary graft failure, acute and chronic Graft versus Host Disease (GvHD), bacterial viral and fungal infections during the post-transplant phase.

**Results:** One hundred and four patients underwent hematopoietic stem cell transplantation. Median age of patients was 12.5years (3-45 years). Stem cell source was peripheral blood in 55(61%), bone marrow in 37(39%) and both in 13 (12.5%) patients. Mean stem cell dose was  $4.8 \pm 2.9$  cells/kg recipient weight. Overall survival at 6 years was 63%. Primary and secondary graft failure occurred in 15% and 16% of patients respectively. Acute GvHD of grade I-II and grade III-IV GvHD occurred in 4/104 (3.8%) and 2/104 (1.9%) patients respectively. Chronic GvHD was observed in 6/92 (6.1%) of patients. Fungal and bacterial infections were observed in 6.1% and 15.5% respectively. CMV-reactivation occurred in 11% patients but CMV disease (CMV pneumonitis) was observed in one patient only. BKV associated hemorrhagic cystitis was observed in 2/104 (1.9%) patients, managed with conservative treatment.

**Conclusion:** Overall survival and quality of life of aplastic anemia patients have dramatically improved with the advent of stem cell transplant in Pakistan. Transplant program needs further expansion in order to cater to the needs of patients coming from different regions of country.

**Keywords:** Hematopoietic stem cell transplantation, Aplastic anemia, Infections, Graft versus Host Disease

## OPTIMIZING CD3 CELL DOSE IN CHILDREN UNDERGOING UNMANIPULATED HAPLOIDENTICAL STEM CELL TRANSPLANTATION WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE

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**Background/Objectives:** Haploidentical hematopoietic stem cell transplantation (HSCT) with post-transplant cyclophosphamide (PTCy) is a technique using T replete unmanipulated stem cell transplantation for the treatment of both malignant and benign hematological disorders. Optimal numbers of CD3 cells are essential for engraftment and sustaining a durable graft.

**Design/Methods:** We performed a retrospective analysis of case records in children less than 18 years undergoing haploidentical HSCT with PTCy from January 2014 to December 2018. Data on the CD3 cells infused and its impact on engraftment was analyzed.

**Results:** Of the total of 89 children transplanted, 66% had a benign disorder, and 34% had a malignant disease. The conditioning regimen was myeloablative in 13% and reduced intensity in 86% of the children. The mean CD34 dose was  $5.22 \times 10^6/\text{kg}$ . The source of stem cells was peripheral blood in 80% and bone marrow in 20% of children. Drawing a ROC curve, we had observed that the area under ROC was 0.606 and deriving a cut off of  $1.54 \times 10^8/\text{kg}$  CD3 cells helped to distinguish between engraftment and primary graft failure with a sensitivity of 50% and specificity of 73%. The mean CD3 cell dose in those who had engrafted was  $1.6 \times 10^8/\text{kg}$ , and those with graft failure was  $1.2 \times 10^8/\text{kg}$ . Seven children had died before engraftment. Of the 82 children who had survived beyond D+28, 11 (13%) had primary graft failure, of which 72.7% had received a CD3 dose of fewer than  $1.5 \times 10^8/\text{kg}$ .

**Conclusions:** A minimum CD3 cell dose of  $1.5 \times 10^8/\text{kg}$  recipient body weight is essential to optimize engraftment in children undergoing haploidentical HSCT with unmanipulated stem cells and PTCy. The above analysis has helped us modify the policy in our unit to optimize CD3 dose in the graft in addition to CD34 dose to prevent graft failure/rejection.

**Keywords:** Haploidentical, HSCT, post transplant cyclophosphamide, CD3 count

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PE-001

## A CASE OF LATE-ONSET SINUSOIDAL OBSTRUCTION SYNDROME AFTER PONATINIB ADMINISTRATION

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**Background:** Sinusoidal obstruction syndrome (SOS) is a potentially life-threatening complication of hematopoietic stem cell transplantation (HSCT). The European Society for Bone and Marrow Transplantation (EBMT) recently proposed revised diagnostic criteria for SOS, which defined late-onset SOS as occurring >21 days after HSCT.

**Case:** A 53-year-old woman received an umbilical cord blood transplantation for relapsed Philadelphia chromosome-positive acute lymphoblastic leukemia with a T315I BCR-ABL mutation from a 5/8 allele-matched donor. The conditioning regimen consisted of fludarabine (120 mg/m<sup>2</sup>) and total body irradiation (12 Gy). Tacrolimus and mycophenolate mofetil were used for graft-versus-host disease (GVHD) prophylaxis, and ursodeoxycholic acid was used for SOS prophylaxis. Neutrophil engraftment was successfully achieved on day 18 and bone marrow examination on day 34 revealed molecular complete remission and complete donor chimerism. On day 61, however, molecular relapse was detected, and ponatinib was started. The patient also developed diuretic-resistant fluid retention, such as pleuroperitoneal fluid, as well as acute GVHD of the gut. These symptoms were temporarily improved with methylprednisolone. However, fluid retention was again exacerbated around day 130, followed by the emergence of jaundice. Despite intensive care, she died from multiple organ failure on day 198. An autopsy was performed, and histopathological examination of the liver revealed massive centrilobular congestion, necrosis, and complete fibrous obstruction of the central vein. These findings lead to the pathological diagnosis of SOS.

**Discussion and Conclusion:** Late-onset SOS is a very rare complication and its mechanism is unknown. Moreover, this is the first case in which ponatinib treatment after HSCT was considered to contribute to the development of late-onset SOS. It is widely known that tyrosine kinase inhibitors (TKI), such as ponatinib, may cause vascular endothelial dysfunction. To confirm the precise mechanism of late-onset SOS development, basic studies are required on the relationship between TKI and intra-sinusoidal cells.

**Keywords:** late-onset SOS, sinusoidal obstruction syndrome, ponatinib, Acute lymphoblastic leukemia

## ACUTE LYMPHOBLASTIC LEUKEMIA DETECTION USING DIGITAL IMAGE PROCESSING TECHNIQUES

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**Purpose or Background:** Leukemia is a cancer that starts in the blood-forming cells of the bone marrow, the spongy tissue inside bones where blood cells are made. There are several type of leukemia, one of them well-known as Acute lymphoblastic leukemia (ALL), a cancer that starts from the early version of white blood cells called lymphocytes in the bone marrow. It can spread to different parts of the body rapidly. Finding the cancer early makes it easier to treat. It can be a fatal disease if not diagnosed at the earlier stage, in a few months it would probably be deadly. Each year, the number of new cases of acute lymphoblastic leukemia increased. The cancer is detected through screening of blood and bone marrow smears by pathologists. But manual examination of blood samples is a time consuming and less accurate as well as limited by human error risks.

**Method or Case:** In this paper, several articles were selected. The search for articles includes the following criteria; the articles should be published in the last 10 years from 2009 to 2019 and discuss about acute lymphoblastic leukemia detection using image processing.

**Results or Progress:** Automatic detection with digital image processing can process images and then analyze to obtain more optimal results. The steps of detecting the disease using image processing technique mainly divided into four stages, namely preprocessing, Segmentation, Feature Extraction and Classification.

**Conclusion or Discussion:** Automatic detection system with digital image processing is faster and more accurate than manual detection.

**Keywords:** image processing, Acute lymphoblastic leukemia

## ALLOGENIC HAEMATOPOIETIC STEM CELL TRANSPLANTATION FOR B-ACUTE LYMPHOBLASTIC LEUKAEMIA (B-ALL) IN ADULTS: A SINGLE CENTRE EXPERIENCE

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**Introduction:** Acute lymphoblastic leukemia (ALL) is an uncommon blood malignancy in adults. In contrast to childhood ALL, survival rate were dismay in adults. Allogenic haemopoietic cell transplantation (HCT) is a potentially curative therapeutic modality for adults with ALL.

**Objective:** This study aimed to investigate the treatment outcome of adult with B lineage ALL patients who undergone allogenic HCT in Ampang Hospital, a tertiary national referral centre in Malaysia.

**Methods:** Data was retrospectively collected and analysed for all adult patients ( $\geq 12$  years) with B lineage ALL who undergone HCT from 2006 till 2018.

**Results:** A total of 176 adult patients were identified with more male (52.8%) than female. Majority of them were matched sibling HCT (82.4%). Median age of transplant was 22 years old (range 12-59). Seventy-four of them (42%) were Philadelphia positive. Fifty five percent of the patients (n=97) are in the high-risk group. Average stem cell dose infused were  $4.9 \times 10^6/\text{kg}$  with median engraftment time of 14 days.

The 3-year overall survival (OS) and event free survival (EFS) was 51.8% and 49.7% respectively. The two main causes of death were disease progression (60.5%) and transplant related (39.5%) such as infection and graft versus host disease. Multivariate analysis showed that high-risk group and patients transplanted in CR>1 were independent prognostic factor for inferior OS and EFS. The 2012-2018 transplanted cohort showed a superior 3-year overall survival compared with the 2006-2011 cohort (57.1% v 34.0%;  $P < 0.01$ ). This is likely due to better selection of patients, improved supportive care and availability of potent tyrosine kinase inhibitor for PH+ ALL patients.

**Conclusion:** There has been improvement in outcome of patients with ALL who were transplanted. Better treatment outcome can be achieved with improvement in monitoring, treatment adherence and accessibility to novel agents.

**Keywords:** B-acute lymphoblastic leukemia, Allogenic Stem Cell Transplantation, Survival, Malaysia



## COMPARISON OF AUTOLOGOUS VERSUS MATCHED SIBLING DONOR STEM CELL TRANSPLANTATION FOR PATIENTS WITH PHILADELPHIA CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

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**Purpose:** This study was to compare the efficacy of autologous stem cell transplantation(SCT) with matched sibling donor(MSD)-SCT in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) in the era of tyrosine kinase inhibitors (TKIs) and to find out the patients who were more eligible for auto-SCT.

**Method:** We retrospectively investigated the outcomes of 78 adult patients with PH+ ALL who received either auto-SCT or MSD-SCT in our center from Jan 2008 to Dec 2017.

**Results:** The estimated relapse rates(RR) at 3 years were 45.7% after auto-SCT(n = 31) and 27.2% after MSD-SCT(n = 47) (P = 0.127) and the non-relapse mortality(NRM) rate were 17.0% and 3.2% ( P = 0.072 ). The estimated leukemia-free survival(LFS) were 51.1% and 55.8% (P = 0.803), while overall survival(OS) rates were 71.8% and 74.1% (P = 0.919), respectively. By multivariate analysis, achievement of complete molecular response (CMR) within 3 months and sustaining CMR up to transplantation(s3CMR) was associated with lower risk of RR (hazard ratio [HR], 3.581, P = 0.004) and higher LFS ([HR], 2.439, P = 0.015). In auto-SCT group, patients with s3CMR demonstrated significantly higher OS (84.0% vs. 40.0%, P = 0.029), higher LFS (70.3% vs. 20.0%, P = 0.020) and lower relapse rate (RR) (24.9% vs. 80.0 %, P = 0.008) as compared to non-s3CMR patients. In MSD-SCT group, the s3CMR only correlated with lower RR (14.4 % vs. 39.6%, P = 0.039) and the OS/LFS was similar between s3CMR patients and non-s3CMR patients.

**Conclusion:** Auto-SCT with maintenance therapy including TKIs after transplant appears to be an attractive treatment option for patients with Ph+ ALL especially for those s3CMR was kept up to transplant. For non-s3CMR patients, allogeneic transplantation may be more effective from lower relapse.

**Keywords:** autologous, matched sibling donor, stem cell transplantation, Philadelphia chromosome-positive, acute lymphoblastic leukemia, sustaining complete molecular response

## EXTRAMEDULLARY RELAPSES OF ACUTE LYMPHOBLASTIC LEUKEMIA AFTER ALLOGENEIC STEM CELL TRANSPLANTATION: CLINICAL CHARACTERISTICS, INCIDENCE, SURVIVAL OUTCOMES AND RISK FACTORS

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**Purpose or Background:** The extramedullary relapse (EMR) of acute lymphoblastic leukemia (ALL) after allogeneic hematopoietic stem cell transplantation (allo-HSCT) remained challenging. Data on EMR in ALL patients are limited.

**Method or Case:** We retrospectively analyzed 314 ALL patients underwent allo-HSCT in our center from 2008 to 2017. Among these patients, 295 (93.9%) have achieved complete response status (CR) before transplantation, consisted of 244 (82.7%) patients in CR1, 44 (14.9%) patients in CR2, 6 (2.0%) patients in CR3, 1 (0.34%) patient in CR4, while 19 (6.1%) patients remained unremitment. They all received myeloablative (MA) conditioning regimen. BMR was defined as bone marrow involvement only; EMR was defined as isolated extramedullary involvement or combined with BM involvement in this research.

**Results or Progress:** 99 (31.5%) patients experienced disease relapse, 54 (54.5%) had BMR, and 45 (45.5%) had EMR. The median overall survival (OS) for all relapses after transplantation was 15 months (95% CI 12.17-18.30), and BMR group was 12.5 months (95% CI 9.75-16.13), and 18.7 months for the EMR group (95% CI 13.87-27.77) ( $p=0.004$ ). The analysis of 5-year cumulative incidence of EMR (CEMRI) showed matched sibling donor (MSD) HSCT was more likely to develop EMR than haploidentical-related donor (HRD) HSCT and unrelated donor (URD) HSCT ( $p=0.032$ , CEMRI=23.34%, 6.67%, 15.56%, respectively). In univariate analysis, prior EMD ( $p=0.004$ ), time from allo-HSCT to relapse ( $\geq 12$  vs  $< 12$  months) ( $p<0.001$ ), were associated with an increased risk of EMR. Multivariate analysis revealed that prior EMD ( $p=0.009$ , RR=1.718, 95% CI 1.148-2.570), time from allo-HSCT to relapse ( $\geq 12$  vs  $< 12$  months) ( $p<0.001$ , RR=4.668, 95% CI 2.096-10.389), time from diagnosis to allo-HSCT ( $\geq 6$  vs  $< 6$  months) ( $p=0.047$ , RR=1.937, 95% CI 1.010-3.716), are independent factors contributing to EMR.

**Conclusion or Discussion:** Compared to BMR, EMR after allo-HSCT have better survival in acute lymphoblastic leukemia patients.

**Keywords:** Acute lymphoblastic leukemia, Allogeneic hematopoietic stem cell transplantation, Extramedullary relapse

## FACTORS RELATED TO QUALITY OF LIFE OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA WHO UNDERGO CHEMOTHERAPY

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**Background:** Acute Lymphoblastic Leukemia (also called ALL or Acute Lymphocytic Leukemia) is a cancer of the blood and bone marrow. This type of cancer usually gets worse quickly if it is not treated. ALL is a type of leukemia that is most prevalent among children which is around 75-80%. The progress of chemotherapy for ALL has increased the survival rate for this cancer. Chemotherapy is the treatment of cancer with a long period of time and most often done which can cause side effects that interfere with the function of physical and psychosocial function. This study aimed to identify factors that are related to the quality of life of children with acute lymphoblastic leukemia who undergo chemotherapy in several hospitals in Indonesia.

**Method:** The method used was studying secondary data from published journals. Of the several journals collected, 12 articles were selected. The search for articles included the following criteria; the articles must be published in the last 8 years (from 2010-2018) and the ALL patients conducted in Indonesia.

**Result:** Based on the dependent variable, the length of life of the patients is often not accompanied by the better quality of life due to chemotherapy side effects towards patients' physical and psychosocial conditions. In Indonesia the ALL is the highest ranked cancer in children that causes of death in children. The results showed that there was correlation between chemotherapy phases and nurses roles with generic quality of life.

**Conclusion:** It is recommended for health care provider to improve outreach to the community, especially about the associated factors of ALL. Thus, there is a need to improve nurses' roles through education and training regarding chemotherapy management and its side effects for ALL.

**Keywords:** Chemotherapy Phases, Quality of Life, Acute Lymphoblastic Leukemia, Indonesia

PE-008

## HAPLOIDENTICAL COMPARED WITH MATCHED SIBLING AND UNRELATED DONOR ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR ACUTE LYMPHOBLASTIC LEUKEMIA : EFFICACY AND SAFETY ANALYSIS

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**Purpose or Background:** Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an important method to treat acute lymphoblastic leukemia (ALL) patients. We compared outcomes of allo-HSCT performed to treat ALL using matched sibling donor (MSD), unrelated donors (URD) and haploidentical related donors (HRD) and to analyze the risk factors which have effects on survival after allo-HSCT.

**Method or Case:** We retrospectively analyzed 211 patients with ALL who received allo-HSCT at our center from January 2010 to December 2016. 116 men and 95 women. The median age was 27 (range 11-54) years old. There were 69 standard-risk patients, 142 high-risk patients. 37 patients underwent MSD-HSCT, 52 underwent URD-HSCT and 122 underwent HRD-HSCT. Engraftment, graft-versus-host disease (GVHD), overall survival (OS), leukemia free survival (LFS), relapse and non-relapse mortality (NRM) were compared among the three groups.

**Results or Progress:** The median follow-up was 31.7 (range 0.4-107.0) months. The 15-day engraftment rate of neutrophils(ANC) in the HRD-HSCT were lower than that in the MSD-HSCT and URD-HSCT ( $P=0.001$ ,  $P<0.001$ ) ; The 15-day engraftment rate of platelets (PLT) in the HRD-HSCT were lower than that in the MSD-HSCT and URD-HSCT ( $P=0.025$ ,  $P=0.002$ ). The incidences of +100 days grade II to IV aGVHD in MSD-HSCT, HRD-HSCT and URD-HSCT were 10.8%, 33.6% and 26.9%, respectively, and the MSD-HSCT was associated with a lower incidence of grade II to IV aGVHD compared with HRD-HSCT ( $P=0.004$ ) and URD-HSCT ( $P=0.048$ ). The incidence of grade II to IV aGVHD in the URD-HSCT was not different from HRD-HSCT ( $P=0.345$ ). There was no difference in grade III to IV aGVHD incidence between the three groups ( $P>0.05$ ). The five year NRM in MSD-HSCT, HRD-HSCT and URD-HSCT were 6.0%, 13.1% and 11.5%, respectively, and it did not differ among three groups ( $P>0.05$ ). The five year cumulative relapse rate after allo-HSCT in sibling, haploidentical and unrelated donor were 51.4%, 32.4% and 28.8%, respectively, the MSD-HSCT was associated with a higher incidence of five year cumulative relapse rate compared with HRD-HSCT and URD-HSCT ( $P=0.030$ ,  $P=0.025$ ). There was no difference in the five year cumulative relapses rate between the three groups in 163 ALL patients who were in CR1 status. For MSD-HSCT, the five year OS

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and LFS were 52.2% and 42.7% respectively. For HRD-HSCT, the five year OS and LFS were 58.4% and 54.5% respectively. For URD-HSCT, the five year OS and LFS were 61.5% and 59.6% respectively. Statistical analysis showed that the five year OS and LFS had no statistical differences between the three groups ( $P > 0.05$ ). On multivariable analysis, high risk disease, unremission status and grade III to IV aGVHD were independent risk factors on survival after allo-HSCT.

**Conclusion or Discussion:** Our data indicate that HRD-HSCT results in outcomes equivalent to MSD-HSCT for ALL. HRD-HSCT could be a valid alternative for ALL patients lacking a sibling donor.

**Keywords:** Haploidentical donors, sibling donors, unrelated donors, allogeneic hematopoietic stem cell transplantation, acute lymphoblastic leukemia

PE-009

## NOVEL POTENTIAL TREATMENT MODALITIES FOR EBF1-PDGFRB FUSION GENE POSITIVE B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA-TWO CASES REPORTS

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**Purpose or Background:** To investigate the clinical characteristics and therapeutic effect of B-cell precursor acute lymphoblastic leukemia (BCP-ALL) with EBF1-PDGFRB fusion gene positive patients.

**Method or Case:** Retrospective analysis of diagnosis and treatment of two patients who diagnosed BCP-ALL with EBF1-PDGFRB fusion gene positive.

**Results or Progress:** One patient, a boy fourteen years old, his white blood cell count(WBC) was  $50-60 \times 10^9/L$ . IKZF 3-8(IK 6) mutation positive, relapsed two times after treatment by chemotherapy and achieved complete remission(CR), who had testicular extramedullary leukemia simultaneously; the other patient, a boy fifteen years old, his WBC was  $46.66 \times 10^9/L$ . IKZF 3-8(IK 6) mutation positive too, who was primary refractory BCP-ALL had not achieved CR after three courses of chemotherapy. Because the leukemia cells of the two patients were all CD19 positive through flow cytometry (FCM), so two patients all accepted the second-generation CD19-directed chimeric antigen receptor T cells (CD19 CAR-T) treatment. Finally, two patients all achieved complete morphological remission, FCM proved that the minimal residual disease (MRD) of the two patients was negative.

**Conclusion or Discussion:** BCP-ALL with EBF1-PDGFRB fusion gene positive belongs to Philadelphia-like (Ph-like) or BCR-ABL1-like ALL. These patients are almost teenager and their average WBC is  $40-50 \times 10^9/L$ . They have the characteristics of poor prognosis and easy recurrence, and they are refractory to conventional chemotherapy and achieve complete response when treated with the tyrosine kinase inhibitor(TKI) imatinib combined with chemotherapy probably. So once CR, these patients should receive hematopoietic stem cell transplantation(HSCT). Through our experience, if the disease recurrence, CART cell therapy can make these patients reach CR again and then bridge to HSCT.

**Keywords:** B ALL, EBF1-PDGFRB, ph-like ALL, ALL, leukemia

## PROGNOSIS FACTORS FOR ACUTE LYMPHOBLASTIC LEUKEMIA IN INDONESIAN'S CHILDREN

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**Purpose or Background:** Acute Lymphoblastic Leukemia (ALL) is the most common hematological malignancy in children. This disease can be fatal, where cells in normal conditions develop into lymphocytes turn malignant and will rapidly increase normal cells in the bone marrow. ALL is the most common leukemia in children. This type of leukemia constitutes 25% of all types of cancer that affect children under the age of 15 years. ALL causes lymphocyte function to be inhibited so that it forms obstructed lymphoid issue, even though this issue is the most important in the immune system. This causes sufferers to be susceptible to various diseases and get infections. The purpose of this study was to study the prognosis factors for acute lymphoblastic leukemia in Indonesian's children.

**Method or Case:** The method was used an electronic database of published journals. Nine of articles from several journals were selected in this study. These articles were published from 2009-2019, the sample of this study was patients with acute lymphoblastic leukemia in Indonesian's children.

**Results or Progress:** Based on the dependent variable, found 5 prognostic factors for acute lymphoblastic leukemia in children. The prognostic factor are gene fusion TEL-AML1, BCR-ABL ALL type, E2A-PBX1, ALL with CD10 negative, children aged <1 year and > 10 years, and leukocyte counts > 50x10<sup>9</sup> / L, while the factors that influence this prognosis are obesity. Other studies have shown that C677T polymorphism gene MTHFR is not an independent prognostic factor in children with ALL.

**Conclusion or Discussion:** Based on the results of the study, the treatment of ALL patients can be done earlier by knowing the prognosis factor of ALL patients in children.

**Keywords:** Prognosis, Acute Lymphoblastic Leukemia, Indonesian's children

PE-011

## SUCCESSFUL COMBINED TREATMENT OF BLINATUMOMAB AND DONOR LYMPHOCYTE INFUSION AFTER HAPLOIDENTICAL HEMATOPOIETIC CELL TRANSPLANTATION IN A RELAPSED PH+ALL PATIENT WITH BCR/ABL1 COMPOUND MUTATION.

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**Background:** Optimal treatment for relapsed acute Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) with T315I mutation after allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains unclear.

**Case:** We report a relapsed Ph+ALL case after allo-HSCT from haploidentical donor with successful treatment of blinatumomab with donor lymphocyte infusion (DLI). A 57-year-old female was admitted to our hematology department with the diagnosis of Ph+ALL. She achieved first molecular remission after induction therapy (JALSG Ph+ALL208IMA regimen). However, she experienced first molecular relapse during the consolidation phase. Because mutation analysis of the ABL1 gene revealed T315I mutation, ponatinib was administered, which resulted in second molecular remission. During the interruption of ponatinib due to drug eruption, she experienced molecular relapse again; second mutation analysis of the gene revealed compound mutation involving T315I, E279K and Y253H. Immediately after the second molecular relapse, she received allo-HSCT from haploidentical donor following the conditioning regimen with fludarabine (150 mg/m<sup>2</sup>), busulfan (12.8 mg/kg) and total body irradiation (4 Gy) and post-transplant cyclophosphamide (Cy). Neutrophil engraftment was achieved on day 16, and minor BCR/ABL1 was not detected by PCR analysis in bone marrow sample on day 42, indicating third molecular remission. While she developed acute graft versus host disease (GVHD; Grade 2, skin stage 3, gut stage 1), the topical steroid was effective for it. One month after post-transplant maintenance therapy of ponatinib, she experienced a hematological relapse (day 291). Chimerism analysis of CD3-positive T-cells showed full-donor chimerism at that time. After the lymphdepletion therapy with Cy and prednisolone, blinatumomab was administered, resulting in fourth molecular remission. One course of DLI (500,000 cells/kg, CD3-positive T-cell) following second blinatumomab treatment kept her remission without severe adverse events.

**Conclusion:** Our successful case suggests that blinatumomab and DLI is an effective salvage therapy even in relapsed Ph+ALL after allo-HSCT with BCR/ABL1 compound mutation.

**Keywords:** Acute lymphoblastic leukemia, T315I mutation, Bi-specific T-cell engagers, Donor lymphocyte infusion



## SUCCESSFUL HAPLOIDENTIC BONE MARROW TRANSPLANTATION WITH INOTUZUMAB OZOGAMICIN IN PATIENT WITH RELAPSED AND RESISTANT B CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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**Purpose or Background:** Although chemotherapeutic(CT) agents that used in the treatment of acute lymphoblastic leukemia(ALL) increase survival, the results are still weak. Long-term survival with CT's in relapse ALL cases is difficult and the prognosis is very weak. Inotuzumab ozogamicin is an anti-CD 22 monoclonal antibody and it has the potential to reduce the overall toxicity of intensive regimens for ALL, as well as to possibly increase the number of patients who may achieve a state of minimal residual disease.

**Aims:** We aimed to present a case of successful haploidentical bone marrow transplantation in a recurrent B-ALL patient who was in remission with inotuzumab ozogamicin.

**Case description:** 26-year-old male patient was diagnosed with B-cell ALL in December 2017. After the HOELZER CT protocol was started, maintenance treatment was continued. In the fifth month of treatment, FLAG CT protocol was started cause of recurrence was seen on 5% blast detection in peripheral blood smear. In August 2018, inotuzumab ozogamicin treatment was started and six cures were completed because the patient was not in remission. In September 2018, He had gone Haploidentical bone marrow transplantation from his sibling donor(8/10) with Defibrotid prophylaxis for Veno-Occlusive Disease(VOD)s. He engrafted successfully and chimerism was 99.85% in 30th days of transplantation. He is 60th day of transplantation and in a remission.

**Results or Progress:** Bone marrow transplantation cannot be performed since the complete response cannot be achieved in patients with relapse and resistant B-ALL. In these patients, new therapies targeting malignant lymphoblasts are needed. Inotuzumab ozogamicin is a monoclonal antibody drug conjugate that targets CD22 antigen on malignant lymphoblasts. In many studies, it has been shown that Inotuzumab ozogamicin is effective and reliable anti-tumor activity in adults with recurrent and resistant CD22 positive ALL. However, monoclonal antibody drug conjugates have been shown to be associated with VOD's. For this purpose, we used Defibrotid to protect our patient from VOD.

**Conclusion or Discussion:** Treatment with combination CT regimens in B-ALL is suboptimal and long-term survival is achieved in only 30-40% of patients. Targeted molecular therapy and new regimens are needed in relapse and resistant patients. At this point, Inotuzumab ozogamicin is an anti-CD-22 monoclonal antibody, as in our case, it provides remission in recurrent and resistant B-ALL patients and allows patients to complete their treatment with an allogeneic transplant from a fully compatible donor.

**Keywords:** Acute lymphoblastic leukemia, Allogeneic bone marrow transplant, inotuzumab ozogamicin, VOD, Defibrotide

PE-013

## THE CLINICAL OUTCOME OF THE PATIENTS RECEIVING BLINATUMOMAB FOLLOWED BY ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION – A SINGLE-CENTER EXPERIENCE

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**Background:** The patients with relapse and/or refractory B cell acute lymphoblastic leukemia (B-ALL) have dismal prognosis. The application of blinatumomab, a bispecific antibody guiding CD3<sup>+</sup> cytotoxic T cells to kills the CD19<sup>+</sup> leukemic cells, dramatically improves the outcome. In our study, we analyzed the clinical outcome of the patients receiving blinatumomab followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT).

**Methods:** We retrospectively collected the clinical information from the patients receiving blinatumomab followed by allo-HSCT at the National Taiwan University Hospital during 2017 to 2019.

**Results:** Twenty-nine patients received blinatumomab between 2017 and 2019, and 24 of them were diagnosed as ALL. Nine patients with ALL, including four male and five females, underwent allo-HSCT after blinatumomab. One patient was diagnosed as Philadelphia chromosome-positive ALL (Ph<sup>+</sup> ALL). The median age was 41 years (range, 23 to 59 years). Before the receiving blinatumomab, the median line of treatments was two. One patient with Ph<sup>+</sup> ALL received tyrosine kinase inhibitor (dasatinib and nilotinib), and another one patient received rituximab. Three patients already underwent allo-HSCT before blinatumomab. The median cycle of blinatumomab was two. All patients had their best response of blinatumomab in the end of the first cycle. Seven patients had complete remission (CR) without minimal residual diseases (MRD), and two patients had CR with MRD detected by the flow cytometry. Two patients had relapse before allo-HSCT, and one had relapse after allo-HSCT. The median duration between blinatumomab and allo-HSCT was 98 days. The median follow-up duration was 411 days. The one-year overall survival was 83.3%, and two-year was 66.7%. The one-year relapse free survival was 62.2%.

**Conclusions:** Blinatumomab improves the outcome of the patients with R/R B-ALL. Further, the R/R B-ALL patients receiving blinatumomab followed by allo-HSCT also had better survival compared with other patients.

**Keywords:** acute lymphoblastic leukemia, blinatumomab, allogeneic hematopoietic stem cell transplantation

## 4-AMINOQUINOLINE 1,3,5-TRIAZINE INDUCES APOPTOSIS VIA ACTIVATION OF CASPASE AND INHIBITION OF PI3K/AKT/MTOR-KINASE IN HUMAN LEUKEMIC CELLS

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**Background:** Acute myeloid leukemia (AML) is the most common form of acute leukemia. It was responsible for about 85% of adult cases and considered as a foremost cause of cancer related death in young adults. The existing clinical agents to treat AML are associated with a wide range of morbidities and the overall low survival rate due to drug resistance. The aberrant activation of phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) has been implicated as key signalling pathway for the progress AML. Thus, its inhibition offers selective advantage for the innovative therapy against AML.

**Method:** The effect of 4-aminoquinoline 1,3,5-triazine (4-AT) was assessed on the cellular viability of against leukemic cells (HL-60) via MTT assay. The compounds were assayed using Annexin V and propidium iodide (PI), fluorescent microscopy, transwell migration, and cell-cycle analysis against HL-60 cell for the anticancer effect. Western blot analysis was also carried out to analyze the effect of 4-AT on the apoptosis related proteins.

**Results:** 4-AT reduces viability of HL-60 cells in concentration dependent manner. It also showed induction of apoptosis via enhancing the level of late and early apoptotic cells. In western blot analysis, 4-AT causes down-regulation of the anti-apoptotic proteins Bcl-XL and Bcl-2 and up-regulation of the pro-apoptotic proteins Bax, Bid, PARP and caspase-3. The phosphorylation of PI3K, Akt and mTOR was also enhanced by 4-AT in HL-60 cells.

**Conclusion or Discussion:** The data of the present study demonstrated the utility of 4-AT against AML due to significant anticancer activity via induction of apoptosis in leukemic cell together with inhibition of PI3K/Akt/mTOR.

**Keywords:** Synthesis, PI3K-AKT-mTOR, leukemia, apoptosis

PE-015

## AN INTERMEDIATE STAGE OF BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM IN BONE MARROW: A CLINICALLY CHALLENGING CASE REPORT

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**Purpose or Background:** Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic malignancy, derived from precursors of plasmacytoid dendritic cells(PDC), with cutaneous involvement firstly always. The estimated incidence is less than 1% of all acute leukemias. With expression of CD4 and CD56 and specific PDC markers (CD123, CD303, and TCL1) without other special expression of markers for B cells, T cells, myeloid or monocytic cells, and NK cells.

**Method or Case:** A 69-year-old retired worker visited our hospital with multiple nodules throughout the body, which had a previous history of the MDS/CMML. Nodule biopsy (right calf skin): BPDCN was diagnosed. The bone marrow tended to AML at first. The patient took a long time to go from the onset to the diagnosis.

**Results or Progress:** The patient is a typical BPDCN in bone marrow eventually with CD38+, CD34-, CD7+, CD56dim, CD117dim, CD14+, CD64-, CD85K++, CD123+, CD300-, CD36+, CD71dim, CD303dim, CD304+, human leukocyte antigen (HLA)-DR+, MPO-. At first, it was at an intermediate stage in bone marrow of onset, which lack of the typical immunophenotype in the diseased issue, bringing the challenges in diagnosis.

**Conclusion or Discussion:** BPDCN is a rare condition with an aggressive course and a poor prognosis, which often present with skin lesions, should be paid more attention. Flow cytometry and immunohistochemistry are essential for making a diagnosis of BPDCN and distinguishing this from other hematological tumor. What we need to recognize is the disease is an evolving process. More emphasis on long-term monitoring for diseases with unknown diagnosis.

**Keywords:** BPDCN, PDC, AML, cutaneous

## CHARACTERIZATION OF SECONDARY ACUTE MYELOID LEUKEMIA IN KOREA

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**Background:** Secondary acute myeloid leukemia (AML) refers to (1) leukemia evolving from prior antecedent hematologic disease (AHD) or (2) leukemia development as a result of previous exposure to a proven leukemogenic chemotherapeutic agents (therapy-related AML; t-AML). Although secondary AML has traditionally been associated with poor survival, it remains contentious whether secondary AML is an independent prognostic factor. In effort to further refine the characteristics of secondary AML, we have conducted this study.

**Method:** This was a single retrospective, longitudinal cohort study of AML patients over 18 years old diagnosed between January 2010 and December 2015. 549 de novo AML patients were compared with 47 t-AML and 84 AHD-AML for demographics, baseline disease characteristics, treatment details and responses, and survival outcomes.

**Results:** Among the AHD-AML patients, 63% had myelodysplastic syndrome (MDS) followed by myeloproliferative neoplasm (MPN) (24%), aplastic anemia (7%) and MPN/MDS (6%). Among the t-AML patients, the most common previous malignancy was lymphoma (28%) followed by breast cancer (19%). For the whole cohort, the median overall survival (OS) was 41 months. When different AML subtypes were considered, de novo AML had the longest median OS (47 months) compared to t-AML (median OS 18 months,  $P=0.017$ ) or AHD-AML (median OS 21 months,  $P=0.003$ ). Interestingly, when patients were divided into risk groups per cytogenetics, there was no survival differences between AML subtypes in favorable and high risk group. However, in intermediate risk group, despite harboring similar number of patients with normal karyotype across different subtypes, de novo AML had significantly better prognosis compared to t-AML or AHD-AML (Figure). On multivariate analysis, older age ( $\geq 65$  years old) and AML subtype were identified as prognostic factors for OS.

**Conclusion:** Secondary AML should not be automatically interpreted as being poor risk. More sophisticated classification is needed for suitable risk-adaptive treatment and better prognosis.

**Keywords:** secondary acute myeloid leukemia, therapy-related acute myeloid leukemia

PE-017

## COMPARATIVE EVALUATION OF WT1 GENE EXPRESSION AT DIAGNOSIS AND END OF INDUCTION IN ACUTE MYELOID LEUKAEMIA AS BIOMARKER FOR THERAPY RESPONSE

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**Purpose or Background:** Minimal residual disease (MRD) assessment has led to substantial improvement in early recognition of recurrence of acute myeloid leukaemia (AML). Various published studies have stated that over expression of the gene Wilms tumor 1 (WT1) has as poor prognostic marker in acute myeloid leukemia (AML). However, there has been paucity of expression studies of WT1 gene expression in Indian scenario. In this study, a comparative evaluation of WT1 gene expression at the time of diagnosis and at the end of induction has been done.

**Method or Case:** A total of 40 cases of AML having blast count more than equal to 20% in peripheral blood or bone marrow and 5 normal healthy controls were enrolled for this study. Bone marrow aspirates samples were taken at diagnosis (labeled as Day-0) and then post-induction (labeled as Day-28). Hematological workup for counts and flowcytometry based phenotypes was done on both occasions. RNA was extracted out from all the samples. WT1 expression of each sample was done using quantitative real-time PCR, and was normalized against endogenous control gene HBG2, GAPDH, and  $\beta$ 2microglobulin.

**Results or Progress:** The blast count was under remission (Blast $\leq$ 5) in 87.5% i.e. 35/40 cases while 22.5% i.e. 5/40 were not in morphological remission (Blast $>$ 5). The expression of WT1 gene was high at the time of diagnosis and was reduced to significant levels at the end of induction. However, those cases with no morphological remission/increased blast count expression either remain same or increased when compared with normal internal control.

**Conclusion or Discussion:** WT1 gene expression along with blast count can act as good biomarker for assessment of remission. This has significant concordance with blast count AML.

**Keywords:** AML, WT1, MRD

## CONVENTIONAL CYTOGENETIC AND MOLECULAR ANALYSIS IN ACUTE MYELOID LEUKEMIA (AML) AND THEIR ASSOCIATION WITH OVERALL SURVIVAL

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**Purpose or Background:** Conventional cytogenetics is one of the most important diagnostic tools of predicting the overall survival of the patients. Molecular genetics in acute myeloid leukemia (AML) have provided insights into the molecular mechanism of leukemogenesis. In this study we aimed to investigate the impact of cytogenetic and molecular methods on the survival of de novo AML patients in order to achieve a useful marker or test in the process of predicting the disease.

**Method or Case:** Cytogenetics and molecular studies such as, the conventional karyotyping, sequencing and reverse transcriptase real time quantitative PCR (RT-qPCR) were included. Overall Survival calculated by Kaplan-meier technique and the data were analyzed by SPSS.V.19.

**Results or Progress:** Among 80 patients, 36(45%) were female and 44( 55%) were male patients. Patients' median age was 29 years, ranging from 1 to 76 years. The mean overall survival was 19 months (95% CI: 1523 months). The 1 year AML survival rate was 61%. There were significant differences in OS between the NPM1-mutated groups compared to the patients without any mutations (19% versus 61%) ( $p < 0.032$ ).

**Conclusion or Discussion:** This study makes a significant contribution in assessing the prognostic value of cytogenetic and molecular markers. This study showed the heterogeneity of de novo AML that involved various factors and prevalence of distinct cytogenetic subgroups. Our data in comparison with other population-based studies, confirmed a differential distribution of cytogenetic and molecular classification indicating geographic heterogeneity

**Keywords:** Acute Myeloid leukemia (AML),, conventional cytogenetics, chromosomal abnormality

PE-019

## FREQUENCY OF TUMOR LYSIS SYNDROME IN ACUTE LEUKEMIA.

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**Introduction:** Acute leukemia is characterized by the presence of 20% or more blasts in peripheral blood or bone marrow biopsy. It includes both AML & Acute ALL. Tumor lysis syndrome is the most common disease related emergency in patients with leukemia & requires immediate management.

**Objective:** To ascertain the Frequency of TLS in Acute Leukemia.

**Study design:** Cross sectional study.

**Setting:** Department of Hematology/Oncology & BMT, Children Hospital & Institute of Child Health, Lahore, Pakistan.

**Duration of study:** The duration of study was from May 2016 to November 2016.

**Results or Progress:** Results: 111 patients were enrolled in this study. 41 (36.9%) patients were female & 70 (63.1%) were male, with mean age of  $42.8 \pm 15.5$  years. 66 (59.4%) patients were found to have AML & ALL was seen in 45 (40.6%) patients. Tumor lysis in AML was seen in 21 patients (18.9%) of which 15 patients (13.5%) had LTLS & 06 patients (5.4%) had CTLS. Tumor lysis in ALL was seen in 23 patients (20.7%) of which 16 patients (14.4%) had LTLS & 07 patients (6.3%) had CTLS.

**Conclusion or Discussion:** TLS is a frequently common disease related complication in patients with acute leukemia. LTLS is found to be more common than CTLS both in AML & ALL.

**Keywords:** Acute Leukemia, Tumor Lysis Syndrome



## MEGAKARYOCYTE IN PERIPHERAL BLOOD SMEARS IN A CASE OF CHRONIC MYELOID LEUKEMIA

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**Purpose or Background:** Presence of megakaryocytes (MGK) in peripheral blood smear (PBS) is a rare condition. This may be seen in myelodysplastic syndrome. I am presenting a case of CML with lymphoid blast crisis showing MGK in PBS, probably first case report of this kind.

**Method or Case:** The case was picked for study while reporting peripheral blood film.

A sixty year old female presented with generalised weakness for four months, low grade fever for two months and history of weight loss for two months. Pallor, mild hepatosplenomegaly and left cervical lymphadenopathy were present. Hemogram showed Total leukocyte count  $15 \times 10^9 /L$ , Differential count; Blasts 85, Neutrophil 15, Hemoglobin 8.7 gm % and platelet count  $170 \times 10^9/L$ . Peripheral blood smear showed a well formed large megakaryocyte.

Bone marrow aspirate smear examination showed 80% blasts in diluted marrow. Bone marrow biopsy showed hypercellular marrow with near total replacement by blasts CD34+ and CD3-, CD20- & CD138-.

Flowcytometry revealed 51% blasts positive for CD19, CD34, CD10, HLA-DR, dim positive for cCD79a & TdT and negative for CD45, CD20, CD38, CD33, CD13, CD117, CD64, CD3, CD4, CD5, CD7, CD8 & MPO. Diagnosis of ALL was given.

On frequent routine haemogram, the value of platelet count was noticed always higher side ( $> 200 \times 10^9/L$ ). This raised suspicion of any other associated disease.

**Results or Progress:** Cytogenetic study revealed chromosome XY, t (9, 22). RTPCR showed P210 positive. Finally the diagnosis chronic myeloid leukemia with blast crisis was considered. Close differential is Ph+ ALL.

### **Conclusion or Discussion:**

- (1). MGK in PBS may be a presentation of CML.
- (2). Blast crisis may be the first presentation of CML.
- (3). Flowcytometer may not be useful in diagnosis of CML with blast crisis.

**Keywords:** megakaryocytes, peripheral blood, blast crisis

## PROGNOSTIC IMPLICATION OF MONOSOMAL KARYOTYPE IN PATIENTS WITH ACUTE MYELOID LEUKEMIA WHO RECEIVED ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

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**Backgrounds:** Monosomal karyotype (MK), defined as at least two autosomal monosomies or one single autosomal monosomy with one or more structural cytogenetic abnormalities, has been associated with worse outcomes in acute myeloid leukemia (AML). We evaluated the prognostic impact of MK on post-remission outcomes of AML patients receiving allogeneic hematopoietic cell transplantation (HCT) in the first complete remission (CR1).

**Methods:** We retrospectively analyzed 531 adult patients with de novo AML, who received HCT in CR1 between 1995 and 2016. All patients had cytogenetic results at the diagnosis of AML. Patients were classified as having good, intermediate, or poor risk cytogenetics according to the NCCN guideline, and MK status was also determined.

**Results:** MK was observed in 35 patients (6.6%) and 31 of them also had complex karyotype (CK). Compared to patients without MK, those with MK had significantly lower overall survival (OS) (63.8% vs. 14.9%) and event free survival (EFS) (56.0% vs. 12.1%), and higher cumulative incidence of relapse (CIR) (27.8% vs. 76.3%) at 5 years (all,  $P < 0.001$ ). Fifty-nine (11.1%) patients with CK also showed inferior outcomes, but MK was associated with more inferior outcomes than CK without MK. Multivariate analysis demonstrated that MK had significantly adverse impacts on OS (hazard ratio [HR]; 2.507,  $P < 0.001$ ), EFS (HR, 3.959;  $P < 0.001$ ), and CIR (HR, 5.617;  $P < 0.001$ ) after HCT.

**Conclusion:** MK is a major prognostic factor predicting extremely worse post-transplantation outcomes in AML patients who underwent HCT in the first CR.

**Keywords:** monosomal karyotype, monosomal karyotype

## PROPHYLACTIC ANTIFUNGAL AGENTS AT THE INDUCTION CHEMOTHERAPY OF ACUTE MYELOID LEUKEMIA: A REAL WORLD COMPARISON SINGLE CENTER STUDY

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**Background:** To prevent invasive fungal disease (IFD) in acute myeloid leukemia patients, the use of posaconazole as prophylactic antifungal agents has become standard in patients with induction chemotherapy. However, there are few data comparing itraconazole and posaconazole as prophylactic antifungal agents in the real world.

**Method:** Patients were collected from the Soonchunhyang University Seoul Hospital from January 2009 to April 2018 with itraconazole or posaconazole for preventing invasive fungal diseases. Clinical data were reviewed and IFD was diagnosed using revised definition of IFD from European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group.

**Results:** A total of 53 patients were recruited to receive either posaconazole (n = 29) or itraconazole (n = 24). IFD occurred in 7 (29.1%) who used posaconazole and in 6 (20.6%) who used itraconazole as antifungal prophylaxis (P = 0.475). The 100-day mortality rate was 4 (13.8%) in the posaconazole group and 2 (8.3%) in the itraconazole group (P = 0.535). 9 (31.0%) in the posaconazole group and 6 (25.0%) in the itraconazole group failed to take the prophylactic antifungal agents due to persistent neutropenic fever, oral mucositis, and poor intolerance (P = 0.762). Among breakthrough IFDs, 12 (92.3%) had more than intermediate risk in the AML risk stratification, and one (7.7%) case was favorable risk. 12 (92.3%) cases were associated with aspergillus infection and only one (7.7%) case was associated with candida infection.

**Conclusion:** There was no significant difference in the incidence of IFD and 100-day mortality between posaconazole and itraconazole as prophylactic antifungal agents. These results suggest that it is better to observe whether posaconazole is superior to itraconazole.

**Keywords:** Invasive fungal disease, Acute myeloid leukemia, Antifungal prophylaxis, Posaconazole, Itraconazole

PE-024

## PTEN/AKT SIGNALING MEDIATES CHEMORESISTANCE IN REFRACTORY ACUTE MYELOID LEUKEMIA THROUGH ENHANCED GLYCOLYSIS

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**Purpose or Background:** Primary refractory acute myeloid leukemia (AML) and early recurrence of leukemic cells are among the most difficult hurdles in the treatment of AML. Moreover, uncertainties surrounding the molecular mechanism underlying refractory AML create challenges for the development of novel therapeutic drugs. However, growing evidence suggests a contribution of PTEN/AKT signaling to the development of refractory AML. To assess PTEN/AKT signaling in AML, we evaluated two types of AML cell lines: control HL60 cells: and KG1 $\alpha$  cells, a refractory AML cell line that shows idarubicin and AraC resistance.

**Method or Case:** Changes in the expression level of glycolysis- and mitochondrial OXPHOS-related genes and proteins were measured by reverse transcription-quantitative polymerase chain reaction and Western blot analysis, respectively. Mitochondrial oxygen consumption rate and extracellular acidification were measured using an XF24 analyzer. CCK8 assays and AnnexinV/PI staining were used to analyze cell viability and cellular apoptosis, respectively.

**Results or Progress:** We first found that PTEN protein was depleted and AKT phosphorylation levels were elevated in KG1 $\alpha$  cells compared with HL60 cells. These changes were associated with increased expression of glucose transporter 1 and hexokinase 2, and increased lactate production. AKT inhibition decreased proliferation of KG1 $\alpha$  cells and decreased extracellular acidification without affecting HL60 cells. Notably, AKT inhibition increased responsiveness of KG1 $\alpha$  cells to chemotherapy with idarubicin and AraC.

**Conclusion or Discussion:** Taken together, our findings indicate that activation of AKT by a PTEN deficiency sustains the refractory AML status through enhancement of glycolysis and mitochondrial respiration, effects that could be rescued by inhibition of AKT activity.

**Keywords:** Refractory acute myeloid leukemia, chemoresistance, PTEN, AKT, Glycolysis

## RISK FACTORS AND ITS TREATMENT OF ACUTE MYELOGENOUS LEUKEMIA (AML) DISEASE IN INDONESIAN COMMUNITY

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**Purpose or Background:** Acute myeloid leukemia (AML) is a leukemia that occurs in myeloid series, including neutrophils, eosinophils, monocytes, basophils, and megakaryocytes. Leukemia suffers in Indonesia are increasing every year by 5.93%. Risk factors such as gender, age, genetics, poor environmental conditions, people's lifestyles, and high consumption of food from animal proteins can affect of AML. The purpose of this study was to analyze various risk factors and its treatment of the incidence of AML that occurred in Indonesia.

**Method or Case:** The method used was by using electronic data based on journals published in the last five years, from 2014 to 2019, were reviewed.

**Results or Progress:** The results showed there are various risks factors of AML disease that occur in Indonesian community, namely age, gender, genetic, consumption of high sources of animal protein, and bad habits that can increase the risk of AML disease. Previous research explained that, gender factors have significant correlation on the probability of AML in Indonesia, more commonly found in female as much as 51.43% in the age group 20-39 years at 45.71%. The risk factors of AML more patients with female gender rather than male.

**Conclusion or Discussion:** It can conclude that in Indonesia, age, gender, genetic, high consumption of animal protein and bad habits have significant correlation toward AML disease. It is expected that community can do early prevention, such as AML treatment therapy is fast and precise, reducing the frequency of bad habits, balanced food choices and improvements in psychological, social and spiritual.

**Keywords:** Age, AML, Animal protein, Gender, Risk factors, Indonesia

## TRAIL AND CD56 IN AML PROGNOSIS AND THEIR CORRELATION WITH HEMATOLOGICAL AND CLINICAL PARAMETERS

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**Purpose or Background:** The aim of this study was to evaluate any correlation between either tumor necrosis factor related apoptosis inducing ligand (TRAIL) or CD56 expression and some prognostic biological parameters of newly diagnosed acute myeloid leukemia (AML) patients, and their predictive impact on response to induction therapy.

**Method or Case:** This study was conducted on 62 newly diagnosed AML patients, blood counts and flow cytometry (FCM) (using acute leukemia panel in addition to TRAIL and CD56 monoclonal antibodies) were performed on either peripheral blood or bone marrow (BM) blasts, whereas cytogenetic studies including conventional karyotyping and FISH study to determine risk group. The patients' remission status following induction therapy was determined.

**Results or Progress:** TRAIL positive patients had lower median total leukocytic count (TLC) and BM blasts percentage compared to negative ones, while those with positive CD56 showed higher median TLC and BM blasts percentage with lower median hemoglobin level. Complete remission (CR) was achieved in 68.4% patients with negative TRAIL while 66.7% with negative CD56 entered in CR.

**Conclusion or Discussion:** TRAIL / CD56 expression on myeloblasts could constitute useful biomarkers of AML disease activity and response to therapy in addition to correlation with other prognostic hematological parameters of AML patients.

**Keywords:** Acute myeloid leukemia (AML), Tumor necrosis factor related apoptosis inducing ligand (TRAIL), Bone marrow (BM), Flow cytometry (FCM), Complete remission (CR).

## KOREAN GOVERNMENT ASSIGNED PUBLIC CORD BLOOD BANKS – 2018 ANNUAL REPORT

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**Background:** Cord blood is a useful source of allogeneic hematopoietic stem cell transplantation. Public cord blood bank (CBB) manages donated cord bloods for their processing and storage of cryopreserved cord blood units (CBU) ready for transplantation. The Cord Blood Management and Research Act enacted in July 2011 in Korea. The number of the government-assigned public is four since 2017 CBB.

**Methods:** The yearly report of the number and the characteristics of inventory and transplantation of cord blood units were collected from four public cord blood banks.

**Results:** (1) The number of cryopreserved in four public CBBs is 2,452 units in 2016, 1,965 units in 2017, and 1,797 units in 2018: The yearly average number of total nucleated cell is 11.0X10<sup>8</sup>/unit, 10.6X10<sup>8</sup>/unit, and 10.5X10<sup>8</sup>/unit, respectively: The average number of CD34 positive cell is 3.0x10<sup>6</sup>/unit, 2.8x10<sup>6</sup>/unit, and 2.9x10<sup>6</sup>/unit. The percentage of CD34 among TNC is 0.27%, 0.25%, and 0.27% respectively

(2) The number of CBU used for transplants supplied from three public CBBs is 68 units in 2016, 68 units in 2017, and 66 units in 2018. The average number of total nucleated cell (TNC) is 14.6X10<sup>8</sup>/unit, 14.8X10<sup>8</sup>/unit, and 14.5X10<sup>8</sup>/unit: The average number of CD34 positive cell is 5.7x10<sup>6</sup>/unit, 5.7x10<sup>6</sup>/unit, and 6.9x10<sup>6</sup>/unit: The percentage of CD34 among TNC is 0.38%, 0.37%, and 0.46%, respectively.

**Conclusion:** The number of qualified CBU is steadily increasing. The increase of CBU usage as a hematopoietic stem cell source is in the stationary phase due to development of other transplantation modality. However, the tendency of selection of the highest quality among inventory has existed. The expansion of indication of CBU therapy is needed for the rest of qualified CBU. Although the main body of operation of the four public CBBs is somewhat different, we share the mission of saving lives with CB.

**Keywords:** CORD BLOOD, PUBLIC CORD BLOOD BANK, GOVERNMENT

PE-028

## MECHANICAL CRYOPRESERVATION OF PERIPHERAL BLOOD STEM CELL: INITIAL EXPERIENCE FROM A TERTIARY CARE HOSPITAL

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**Background:** For long term storage of stem cells, peripheral blood stem cells need to be cryopreserved. Here, we report an analysis of first 10 cryopreservation of peripheral-blood stem-cell (PBSC) in mechanical freezers (-80°C) at our center in terms of CD 34+ viability and cell engraftments in those patients.

**Method:** Peripheral blood stem cells (PBSCs) were collected from autologous donors using P1YA kits on Com.tec. A solution of 10% DMSO, 20% human serum albumin with 6% HES was used for cryopreservation of cells. An equal amount of cryoprotective solution was mixed to the PBSC and transferred into Cryobags that were placed in a - 80°C mechanical freezer. The criteria of engraftment was to reach count of  $20 \times 10^9/L$  for platelets and  $0.5 \times 10^9/L$  for neutrophils respectively.

**Results:** All 10 patients were posted for re-transplant (2nd /3rd) and were heavily pre-treated with chemotherapy. Average time duration of storage for cryopreserved stem cells was 27 days (range 10 to 56 days). The initial yield of the products before cryopreservation ranged from  $3 \times 10^6$  to  $10.2 \times 10^6$  per Kg of the patient (mean dose  $7.85 \times 10^6$  per Kg) which decreased to a mean of  $5.95 \times 10^6$  per Kg post thawing of frozen stem cells. Stem cells viability after thawing ranged from 77 percent to 90 percent of total CD 34+ cells. All the patients had neutrophil and platelet engraftment before they were discharged. Days taken for engraftment of neutrophil ranged from 10 to 15 days (mean 11.5 days) whereas for platelets, it ranged from 14 to 43 days (mean 23.5 days).

**Conclusion:** Peripheral blood stem cells can be cryopreserved in mechanical freezers using a solution of 10% DMSO, 20% albumin with 6% HES up till 8 weeks without significant decrease in number and viability of CD34+ cells.

**Keywords:** cryopreservation, stem cells, PBSC



## PLATELET REFRACTORINESS DURING BONE MARROW TRANSPLANTATION, COMPARISON IN APLASTIC ANEMIA AND BETA THALASSEMIA MAJOR PATIENTS. AN EXPERIENCE OF PUBLIC SECTOR BMT UNIT IN AN UNDER DEVELOPED COUNTRY, PAKISTAN.

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**Purpose or Background:** Bone Marrow Transplantation (BMT) is curative treatment modality for many Hematological and oncological diseases. This treatment is very common in developed countries of world but in underdeveloped countries this facility is not available in routine. We have established first Public sector BMT center at the Children Hospital & Institute of Child Health, Lahore, Pakistan in collaboration with NIBD & BMT, Karachi, Pakistan. This BMT center is providing the HSCT facility free of cost to the children of poor families. This unit is financially supported by the Government of Punjab, Pakistan. So we as BMT Physicians have the ethical and moral responsibility to save the expenses and decrease the undue expenditure.

In this regard we have noticed that a handsome amount of money is being consumed for platelet transfusions during Bone Marrow transplantation. Platelet transfusions have greatly reduced the incidence of major haemorrhagic complications during BMT but refractoriness to infused platelets becomes a major clinical problem for many of these patients.

We have reviewed the data of the patients and comparison done for the patients of Aplastic Anemia (AA) and Beta Thalassemia Major (BTM).

**Method or Case:** This study reviewed the data of the patients of both AA and BTM. Total 19 patients have been done BMT of these patients, AA patients were 11 and 08 were of BTM.

As our BMT unit is established as a model for the lowest expenditure for BMT so only the necessary investigations were done. Platelet refractoriness is confirmed by the "lack of platelet count rise ( $> 10,000 \times 10^9 / l$ ) after one hour of a single Mega unit Platelet transfusion. No HPA antigen or antibodies or HLA antibodies identified because of financial constraints.

**Results or Progress:** In our limited experience, the comparison of platelet refractoriness is more common in the patient of beta Thalassemia than that of Aplastic Anemia. The only 2/11 Aplastic Anemia patients showed platelet refractoriness while 6/08 of Beta Thalassemia had platelet refractoriness.

**Conclusion or Discussion:** Our study also directed towards the evidence that the PRBCs transfusion is most likely produced antibodies responsible for platelet refractoriness. Also the BTM patients are immuno-

competent and can produce alloimmunisation for platelets as well along with RBC transfusion.

Aplastic Anemia patients have less Immunocompetency than that of BTM, this can be one reason and other can be the possibility of least number of Blood transfusions during illness (because of urgent Planning for BMT in AA patients).

We recommended to the Hematologists and the Physicians who are involved in the management of BTM patients that the Red cell Extended Grouping/Phenotype and matching should be done surely before putting the patients on chronic PRBCs transfusion therapy. These strategies ultimately decrease the complications of alloimmunisation both in PRBCs and Platelet Transfusion. Hence decrease financial burden on the family as well as on Hospital.

**Keywords:** Aplastic Anemia, Beta ThalassemiaMajor, Bone Marrow Transplantation, Platelet, Refractoriness

## APLASTIC ANEMIA PROBLEM IN INDONESIA

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**Purpose or Background:** Aplastic anemia is hematological abnormality among peripheral pancytopenia, in this condition blood count inadequate. Most cases in aplastic anemia are acquired immune mediated but some cases cause inherited forms. In Indonesia anemia aplastic is not major disease, but can't be ignored because this disease is not only experienced by adults but also children and adolescents. In west Java, a 12-year-old boy suffers from aplastic anemia in 2018, and after that in 2019 a 16 years old boy also suffers from aplastic anemia. in 2014 60% woman suffers from aplastic anemia, case study in RSUP sanglah Denpasar. All case that has been happen need solution, so this paper try to find solution for aplastic anemia and how to manage the disease.

**Method or Case:** This paper use literature review method to find solution for aplastic anemia, and also take secondary data from ministry of health.

**Results or Progress:** There are four part of the solution for aplastic anemia, supportive management, Immunosupresan, medicamentous and Combination drug therapy.

**Conclusion or Discussion:** Aplastic anemia is a serious disease that can occur at any age level, and each solution have different treatment.

**Keywords:** Aolastic anemia, supportive management, Immunosupresan, medicamentous, Combination drug therapy., peripheral pancytopenia

PE-031

## CHALLENGES OF STEM CELL TRANSPLANTATION IN BONE MARROW FAILURE SYNDROMES

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**Background:** Bone marrow failure syndromes are a diverse set of genetic & acquired disorders in which there is inability of the bone marrow to produce sufficient blood cells. There are different pathways discovered in BMF which can lead to cellular apoptosis and can predispose to malignant transformation.

**Method:** The important disorders associated with Inherited Bone Marrow Failure Syndromes (IBMFS) are Fanconi Anaemia, Dyskeratosis Congenita, Shwachman-Diamond Syndrome, Diamond-Blackfan Anaemia and Congenital Dyserythropoietic Anaemia etc. The acquired bone marrow failure includes Aplastic Anaemia, PNH, Myelodysplastic Syndrome (MDS) and Acute Leukemia. In most of these disorders the only curative modality of treatment is haematopoietic stem cell transplantation (HSCT). The selection of the patient, conditioning protocols and post-transplant management of these cases is very challenging.

**Results:** Until now, we performed 353 allogeneic stem cell transplants (matched related) in Aplastic Anaemia. OS is 80.2% & DFS is 73.5%. 16 haploidentical transplants were done in Aplastic Anaemia and DFS is 62.5%. 33 allogeneic stem cell transplants were performed in IBMFS at Armed Forces Bone Marrow Transplant Centre, Rawalpindi. Out of these transplants, 27 patients were of Fanconi Anaemia and 06 kids of Diamond-Blackfan Anaemia. In Fanconi Anaemia, post transplant DFS/OS is 72.7% and TRM is 27.3%, while in Diamond Blackfan Anaemia DFS/OS is 100%.

**Conclusion:** In bone marrow failure syndromes, Hemopoietic Stem Cell Transplantation (HSCT) is the only curative treatment but selection of the patient and refinement in conditioning and follow-up protocols are key to success.

**Keywords:** Inherited Bone Marrow Failure Syndromes, Fanconi Anaemia, Diamond-Blackfan Anaemia, Aplastic Anaemia

PE-032

## FLOW CYTOMETRY, AS FAST AND EFFECTIVE TOOL FOR MONITORING OF HYPER-IGM SYNDROME IN A 13-MONTH-OLD YOUNG BOY WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Purpose or Background:** X-linked Hyper-IgM syndrome (XHIM) is a rare primary immunodeficiency disorders characterized by decreased serum levels of IgG and IgA and normal or elevated IgM levels. This disease caused by mutation in the CD40LG gene which encodes the CD40 ligand (CD40L) protein, also called CD154 predominantly expressed on activated CD4+ T-cells. Hematopoietic stem cell transplantation (HSCT) help to cure of XHIM with opportunistic infections associated with high mortality and morbidity. To examine of CD40L expression can be used not only for the diagnosis of XHIM but also for the monitoring after HSCT.

**Method or Case:** A 4-month-old male infant with Pneumocystis jiroveci pneumonia and acute respiratory distress syndrome was diagnosed XHIM by molecular genetic study. Flow cytometry analysis of activated CD4+T-lymphocytes which in whole blood were stimulated with PMA and ionomycin for 6 hours demonstrated negligible levels of CD40L expression of less than 0.1%. His mother who is carrier of XHIM indicated the partial expression of CD40L

**Results or Progress:** At 13 months of age, he underwent allogenic HSCT from matched unrelated donor. The expression of CD40L on the surface of activated CD4+ T-lymphocytes was assessed on 21 days after HSCT and the result was reported as 25.7% within one day which was suggested apparently successful HSCT. Since then, his chimerism analysis by short tandem repeats showed 99.2% stable engraftment and the genetic analysis by Sanger sequencing revealed his novel mutation (c.415delC, p.Gln139 Serfs\*10) causing XHIM was lost. He has been well for 2 years after HSCT with only temporary pulmonary infection.

**Conclusion or Discussion:** The detection of CD40L expression on activated CD4+ T-lymphocytes in whole blood is as effective in diagnosis of XHIM as genetic test. Additionally, this flow cytometry assay enables independent tool for monitoring of the XHIM patients received HSCT. In XHIM patients, it can be recommended as the fast test for confirmed success of transplantation.

**Keywords:** FLOW CYTOMETRY, HYPER-IGM SYNDROME, HEMATOPOIETIC STEM CELL TRANSPLANTATION

PE-033

## FLUDARABINE CYCLOPHOSPHAMIDE BASED CONDITIONING IS ASSOCIATED WITH GOOD OUTCOMES IN PATIENTS UNDERGOING MATCHED SIBLING DONOR TRANSPLANTS FOR APLASTIC ANAEMIA ESPECIALLY IN LOW RISK PATIENTS

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**Background:** Fludarabine based conditioning protocols are increasingly being used for transplant (SCT) in patients with aplastic anaemia (AA) especially in those who have received multiple transfusions.

**Patients and Methods:** Between 2004 and September 2018, 233 patients with AA underwent SCT at CMC Vellore India using a fludarabine based protocol consisting of Fludarabine [180 mg/m<sup>2</sup> over 6 days] and Cyclophosphamide [120 mg/kg over 2 days]. Few patients received additional ATG. Data on HSCT and outcomes were collected from the institutional database and individual medical records. High risk patients had any of the following risk factors - > 20 transfusions prior to SCT, > 3 months after diagnosis, presence of active infection or major organ bleed and previous exposure to ATG.

**Results:** The median age was 23 years (range: 2 – 58) including 153 boys and 80 females while 78 were children (33.4%). The graft source was Bone marrow in 11 and peripheral blood stem cells in 222. GVHD prophylaxis consisted of cyclosporine and methotrexate mainly with few receiving post-transplant cyclophosphamide. 151 patients were considered as high risk.

Engraftment occurred in 89% with graft failure in 4.2% and early death in 6.8%. Regimen related toxicity (RRT) was seen in 4.7% and included veno-occlusive disease of liver and hemorrhagic cystitis. Acute GVHD (grade 2-4) occurred in 36.5% while chronic GVHD was seen in 58.5%. The 5 year overall survival (OS) for the entire group is 72.8 + 3.1% with higher OS in children (78.4 + 6.1%) compared to adults (67 + 3.9%). 5 yr OS was significantly higher in low risk patients [90.2 + 3.3%] compared to high risk patients [59.6 + 4.4%] [p = 0.001].

**Conclusion:** Fludarabine based conditioning is associated with improved survival following sibling donor HSCT for AA. Taking a patient early to transplant is key to improving outcomes.

**Keywords:** aplastic anemia, Fludarabine, outcomes

## IDENTIFICATION OF THE INTEGRATIVE AND EPIGENETIC GENOMES THE MOLECULAR BASIS OF RESISTANCE TO HYPOMETHYLATING AGENTS TREATMENT IN MYELOYDYSPLASTIC SYNDROMES

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**Purpose or Background:** Myelodysplastic syndrome (MDS) represents a heterogenous group of disorders with a wide spectrum of clinical, morphological, biologic, and genetic characteristics and a tendency to evolve into acute myeloid leukemia (AML). Although hypomethylating agents (HMAs) have been shown to be effective in the treatment of high-risk MDS and AML patients, but they appear to be rapidly relapsing during the treatment of many patients.

**Method or Case:** Since the cause of HMAs resistance is unknown, there are few alternatives to those who do not respond. Therefore, confirming the predictive factors for HMAs resistance may suggest an alternative treatment strategy for relapsed and nonresponsive patients. We used a combination of genomic approaches including genetic typing based on next-generation sequencing and bisulfite sequencing to identify HMAs resistance in myelodysplastic syndrome cells.

**Results or Progress:** Here, we show recent advances in our genetic understanding of MDS, with a particular focus on the emerging role for epigenetic data in clinical management as a potential tool to assist in diagnosis and therapeutic decision-making.

**Conclusion or Discussion:** In summary, this study suggests that patients can predict whether they are resistant to HMA. Therefore, systematic determination of HMAs resistance gene expression may be of great interest to newly diagnosed MDS patients and HMAs treated MDS patients.

**Keywords:** MDS, Methylation, Gene expression profile, Epigenetic

PE-035

## SECOND ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION, AN IMPORTANT RESCUE OPTION FOR GRAFT FAILURE IN CHILDREN WITH ACQUIRED APLASTIC ANEMIA

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**Purpose or Background:** To investigate the efficacy and safety of second allogeneic hematopoietic stem cell transplantation (allo-SHCT) for graft failure (GF) in children with acquired aplastic anemia (AAA).

**Method or Case:** Retrospectively analyzed the clinical data of AAA children receiving second allo-HSCT for GF between July 2002 and December 2017 at Shanghai Children's Medical Center.

**Results or Progress:** Among 283 AAA children who undergoing allo-HSCT, 8 received second allo-HSCT for GF, including 2 primary GF and 6 second GF. 6 patients acquired neutrophil engraftment with median time of 14 (10~26) days. 4 patients acquired platelet engraftment with median time of 15.5 (11~35) days. 1 patient died of infection before engraftment, and 1 patient encountered primary GF. 5 patients developed acute graft versus host disease (GVHD), and 3 patients developed chronic GVHD. After a median follow-up of 17 months, 3 patients died of infection, and the other 5 patients were survival, including two with chronic GVHD.

**Conclusion or Discussion:** Second allo-HSCT is a feasible and effective rescue option for GF in AAA children.

**Keywords:** Graft failure, Aplastic anemia, Hematopoietic stem cell transplantation



PE-036

## CCR9 GUIDES MIGRATION OF MESENCHYMAL STEM CELLS TO THE THYMUS IN MURINE GVHD MODEL: A NOVEL APPROACH TO AMELIORATE GVHD THROUGH THYMUS

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**Background:** Insufficient thymic function of allo-HSCT recipients results in continuous production of alloreactive T cells, which participates in the development of cGVHD. Inefficient homing of systemically infused mesenchymal stem cells (MSCs) limits the efficacy of existing MSCs-based clinical GVHD therapies. Thus, we hypothesized chemokine receptor 9 (CCR9), the receptor that specifically guides migration of T-lineage precursors into thymus, may do the same to MSCs, thereby reducing GVHD by repairing thymus tissue structure and rescuing thymus function.

**Methods:** We carried out studies in vitro and in murine cGVHD model. Radiation-pretreated murine thymic epithelial cells (TECs) were cultured alone or co-cultured with murine MSCs in vitro. CCR9 overexpressed (MSC-CCR9), knocked-down and no-load MSCs were generated and administrated intravenously at dose of  $5 \times 10^5$  cells/infusion at 7th and 21th day post allo-HSCT to the treated groups respectively to compare their thymic homing ability, and therapeutic effects of cGVHD with the untreated group.

**Results:** TEC co-cultured with MSC had a decreased apoptosis and increased proliferation level compared to TEC cultured alone. MSC-CCR9 infusion potently alleviated the clinical signs of cGVHD and prolonged the survival of cGVHD mice. MSC-CCR9 were found to appear in the cortex-medium junction of thymus in a greater amount 24 hours after the first infusion, then distribute throughout thymus and relocate in proximity with TECs, therefore, potently repaired injured TECs and promoted their proliferation and maturation. The number of CD45-CD326+TECs and its proportion of thymus stroma were significantly improved, including CD45-CD326+UEA-1+Aire+ medullary TEC and CD45-CD326+Ly51+ cortical TEC. As for thymocyte, MSC-CCR9 infusion significantly increased the number and proportion of CD4+CD8+T cells and CD4+CD25+Foxp3+ Tregs, which were reported deficiency in GVHD thymus.

**Conclusion:** This study demonstrates that CCR9 guides migration of MSCs to thymus and thus highly intensify their issue repair and immunomodulatory effect to rescue thymus function in cGVHD model.

**Keywords:** Mesenchymal Stem Cells, Allogeneic Hematopoietic Stem Cell Transplantation, Graft-versus-Host Disease, Chemokine receptor 9, Thymus, Thymic Epithelial cells

PE-037

## RESULTS FROM NORTHSTAR AND NORTHSTAR-2 STUDIES OF LENTIGLOBIN GENE THERAPY FOR TRANSFUSION-DEPENDENT B-THALASSEMIA IN NON-B0/B0 GENOTYPES

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**Background:** LentiGlobin, an investigational gene therapy for patients with transfusion-dependent  $\beta$ -thalassemia (TDT), contains autologous CD34+ cells transduced ex vivo with BB305 lentiviral vector (LVV) encoding  $\beta$ -globin with a T87Q substitution. Results of LentiGlobin in patients with TDT and non- $\beta$ 0/ $\beta$ 0 genotypes from the completed Phase 1/2 Northstar (NCT01745120) and ongoing Phase 3 Northstar-2 (NCT02906202, using a refined manufacturing process) studies are reported.

**Methods:** Following G-CSF and plerixafor mobilization, CD34+ cells were transduced with BB305 and infused in patients who received single-agent busulfan myeloablation. Statistics represent median (min-max).

**Results:** Ten and 16 patients with TDT ( $\geq 100$  mL/kg/yr red blood cells [RBCs] or  $\geq 8$  transfusions/yr) and non- $\beta$ 0/ $\beta$ 0 genotypes were treated in Northstar and Northstar-2 studies, respectively, as of 14 September 2018. Median follow-up was 36.0 (29.3-48.1) and 9.3 (0.7-20.4) months, respectively. All patients with  $> 2$  months follow-up had hematopoietic stem cell engraftment.

In Northstar, 8/10 patients had durable transfusion independence (TI; weighted average hemoglobin [Hb]  $\geq 9$  g/dL without RBC transfusions for  $\geq 12$  months). Duration of TI was 38.0 (21.2-43.6) months. Weighted average Hb during TI was 10.2 (9.3-13.2) g/dL.

In Northstar-2, 10/11 patients with  $\geq 3$  months follow-up have stopped transfusions. Hb was 11.1-13.3 g/dL with gene therapy-derived HbAT87Q of 7.7-10.6 g/dL at last visit. Two of 3 evaluable patients achieved TI. Five of 6 patients with  $\geq 1$ -year follow-up had improved myeloid:erythroid ratios (0.18-0.45 to 0.77-1.1).

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The most common post-infusion non-hematologic adverse events in either study ( $\geq$ Grade 3) were stomatitis, febrile neutropenia, irregular menstruation, epistaxis, pyrexia, and liver veno-occlusive disease. There were no deaths, no replication-competent lentivirus detected, and no clonal dominance.

**Conclusion:** Overall, in Northstar, 80% of patients with non- $\beta^0/\beta^0$  genotypes had durable TI. In Northstar-2 using a refined drug product manufacturing process, patients appear to have near-normal Hb. LentiGlobin safety profile is consistent with busulfan myeloablation.

**Keywords:** Beta-thalassemia, gene therapy, lentiviral vector

PE-038

## ADOPTIVE DONOR IMMUNITY PROTECTS RESOLVED HBV REACTIVATION AFTER ALLO-HSCT IN THE WORLD'S LARGEST SINGLE CENTER STUDY

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**Background:** Reactivation of hepatitis B virus (HBV) by reverse seroconversion (HBV-RS) after allogeneic hematopoietic stem cell transplantation (allo-HSCT) could happen in patients with resolved HBV infection (rHBV, defined as negative HBV surface antigen and positive anti-HBV core-antigen antibody), and may cause fatal hepatitis.

**Methods:** In this largest single center cohort, we retrospectively collected 817 consecutive allo-HSCT during 2005 to 2016 from database. We excluded cases with positive HBsAg donors and selected 445 rHBV patients for analysis. The HBV DNA were negative on both recipient and donor side.

**Results:** The 3-year and 5-year cumulative incidence of HBV-RS after allo-HSCT was 8.7% and 10.5%, respectively, with a median 16 months after allo-HSCT. All had concurrent HBV reactivation. HBV flares developed in 19% of HBV-RS cases, but none experienced hepatic failure. Neither did it impact non-relapse mortality or overall survival. Multivariate analysis revealed that patients with donor lacking anti-HB surface-antigen antibody (anti-HBs) protection and extensive chronic graft-versus-host disease (cGVHD) have the highest risk for HBV-RS, with 5-year incidence of 24.2%.

**Conclusion:** Adoptive immunity transfer from the donor seems to have protective effects against HBV-RS, which may alter future donor selection algorithm, and combining the extensive cGVHD provides a good target for risk-adaptive HBV prophylaxis.

**Keywords:** Reverse seroconversion, resolved hepatitis B infection, allogeneic stem cell transplantation, risk factors, hepatitis B, epidemiology

## BKV POLYOMA VIRUS-ASSOCIATED HEMORRHAGIC CYSTITIS AFTER ALLOGENIC STEM CELL TRANSPLANTATION: INCIDENCE, SEVERITY AND RISK FACTORS

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**Background:** BKV, a human polyoma virus, is acquired in childhood and can reactivate after stem cell transplantation. Clinical presentation may vary from being asymptomatic to grade 4 hemorrhagic cystitis. It is one of the frequent causes of late onset hemorrhagic cystitis causing significant morbidity. We aimed to ascertain the incidence of BKV virus positivity in patients undergoing allogeneic stem cell transplant and correlation analysis of various risk factors associated with hemorrhagic cystitis.

**Method:** A non-interventional study was conducted at the National Institute of Blood Institute and Bone Marrow Transplantation from 2017 to 2018 and evaluated the frequency of Serum BKV in patients undergoing allogeneic stem cell transplant from Day+7 to +100. Cyclophosphamide based conditioning regimen was used for Aplastic anaemia and myeloablative conditioning regimens for Thalassemia and malignant disorders. Hemorrhagic cystitis (HC) was diagnosed and graded according to EBMT criteria. BKV disease was diagnosed in the presence of hemorrhagic cystitis (HC) and positive BK virus in plasma sample.

**Results:** A total of 82 patients were included in the study with a median age of 11 years (Range: 1.2-38 years). There was a male preponderance in the present study with 62.2% being males. 76 patients were diagnosed with benign while 6 had malignant disorders. BKV virus positivity was seen in 20 of the 82 patients (24%) of which 85% were male and 25% females. Of these 20 patients, 30% (n=6) patients experienced hemorrhagic cystitis with equal number of patients having grade I-II and grade III-IV HC. The median onset of BKV-HC was observed on day +20.

**Conclusion:** BKV hemorrhagic cystitis is a common cause of potential morbidity after allogeneic stem cell transplantation and has a significant association with male gender and cyclophosphamide-based conditioning regimen.

**Keywords:** hemorrhagic cystitis, allogeneic stem cell transplant, BK polyomavirus, conditioning regimens

## DEVELOPING DEFENSE SYSTEM IN THE ERA OF DRUG RESISTANT BACTERIAL SEPSIS TO IMPROVE OUTCOMES IN CHILDREN UNDERGOING HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN DEVELOPING COUNTRIES

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**Objective:** To study spectrum of bacterial infection, methods for early detection and treatment of bacteremia to reduce sepsis related mortality in children undergoing hematopoietic stem cell transplantation (HSCT).

**Method:** We performed a retrospective analysis in children up to 18 years undergoing HSCT from January 2016 to December 2018, during the neutropenic phase of HSCT. Xpert CARBA-R assay in the stool samples was performed from rectal swab at the time of admission.

**Results:** Of the total 350 children, 43 (12%) had culture-positive sepsis (gram-positive in 20%, gram-negative (GNB) in 80%). The most common organism isolated were Klebsiella pneumonia (KPC) (39%), E.coli (18%) and Pseudomonas species (14%). Nearly 64% of the Klebsiella isolates and 75% of E.coli isolates were carbapenem-resistant (CRO). The sepsis related mortality rate was 10%. Thirty-one percent of the stool samples had CRO with NDM being the most common, followed by NDM and OXA in combination in 13% and KPC bacteria in 0.3%. A significant correlation was noted between CARBA-R in the stool and detection of gram-negative organisms in the blood culture (P-value 0.039). Oral and perianal mucositis (grade II–III) was noted in 83% and 55% children respectively. GNB was isolated in 80% of those with mucositis, with CRO noted in 33% and 45% isolates among those with oral and perianal mucositis respectively. Oral care with aloe vera and cephalexin mouth wash and Sitz bath with mupirocin ointment twice daily for perianal care was given. Among those with progressive perianal mucositis, a combination of mupirocin, clotrimazole and zinc cream alternating with modified lanolin oil are applied locally.

**Conclusion:** Klebsiella pneumonia is the most common organism isolated with 64% of these being CRO. A high index of suspicion and vigilance for mucositis and early interventions have decreased mortality to 10%. Stool CARBA R is a powerful screening tool for early and rational use of antimicrobial agents.

**Keywords:** perianal mucositis, HSCT, carbapenem resistant

## FECAL MICROBIOTA TRANSPLANTATION IN A HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENT COLONIZED WITH CARBAPENEM-RESISTANT ENTEROBACTERIACEAE: A CASE REPORT

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**Purpose or Background:** We report on a hematopoietic stem cell transplant(HSCT) recipient treated with tandem fecal microbiota transplantations (FMT) for carbapenem-resistant enterobacteriaceae (CRE) colonization.

**Method or Case:** A 45-year-old man who underwent HLA-identical sibling allo-HSCT for acute myeloid leukemia(AML-M5b). The patient developed recurrent respiratory and intestinal infection of klebsiella pneumoniae following transplantation. Both anal swab and blood culture indicated MDR klebsiella pneumoniae, which revealed CRE colonization. The patient developed oral chronic graft-versus-host disease (GvHD) and weight loss three months after transplantation. Considering the possibility of intestinal dysbiosis, we performed tandem FMTs with a interval of 3 weeks by nasoduodenal tube. Prior to FMT and one week, one month, two months, six months after FMT , we evaluated the composition of his fecal microbiota using 16S rDNA-based molecular techniques and did stool cultures.

**Results or Progress:** His symptoms and GvHD got controlled and his weight was increasing following FMT. His stool output normalized and showed sustained decolonization without any recurrence of infection at latest follow-up. Shannon index of his intestinal microbiota increased from 2.38 to 3.99, and finally reached the number waving around 3(2.91-3.14), which were similar to the donor(2.93-3.12).This indicted that fecal microbiota of donor had transplanted and patient's intestinal bacterial diversity was increased. We detected the cellular immune function of T cells, B cells and NK cells before and after FMT, no obvious difference were observed.

**Conclusion or Discussion:** This report describes our experience with tandem FMTs in the treatment of a patient with CRE colonization after HSCT, improved his intestinal diversity and survival quality. Despite the favorable outcome, our findings were obtained from a single patient and therefore may be considered preliminary, and his long-term survival will be observed. Further investigation with randomized clinical trials is warranted to validate the efficacy of this procedure for CRE colonization and for broader clinical use.

**Keywords:** Fecal microbiota transplantation, hematopoietic stem cell transplantation, Bone marrow transplant, carbapenem-resistant enterobacteriaceae colonization, Graft-versus-host-disease (GVHD), microbiome

PE-042

## HBSAG ANTIBODY DECREASE THE RISK OF HBV REACTIVATION IN HBV RESOLVED PATIENTS RECEIVING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Background:** HBV reactivation can occur in HBV resolved patients (HBsAg-negative, anti-HBc positive, with or without antibody to HBsAg) during Allogeneic hematopoietic stem cell transplantation (allo-HSCT). It can cause severe liver injury, immunosuppressive drug therapy (ISDT) interruption and even death when HBV reactivation. The risk factors of HBV reactivation in HBV resolved patients receiving allo-HSCT have remained uncertain until now.

**Method:** We retrospectively identified 791 consecutive patients who underwent allo-HSCT from 2008 to 2016 in our single center. Patients or donors who were HbsAg-positive and/or had detectable HBV DNA before HSCT were excluded, leaving 300 HBV resolved patients for analysis.

**Results:** HBV reactivation was identified in 13 patients at a median 588(455-1294) days after allo-HSCT. The 3 and 5 year cumulative incidence of HBV reactivation after allo-HSCT was 4.43% and 5.01%, respectively. The 5-year cumulative incidence of HBV reactivation after allo-HSCT was 3.49% in anti-HBs(+) patients and 12.60% in anti-HBs(-) patients respectively ( $p=0.0034$ ). However, the status of donors' HBsAg antibody didn't significantly influence the 5-year cumulative incidence of HBV reactivation after allo-HSCT (4.85% in anti-HBs(+) donors and 6.00% in anti-HBs(-) donors,  $p=0.523$ ). Multivariate analysis revealed that patients with HBsAg antibody have the lowest risk for HBV reactivation ( $p=0.031$ , hazard ratio [HR]=0.172, 95% confidence interval [CI]=0.035–0.853).

**Conclusion:** HBV reactivation was a late phase complication after allo-HSCT. Anti-HBsAg antibodies play a protective role in HBV-resolved patients receiving HSCT.

**Keywords:** resolved hepatitis B virus infections, reactivation, HSCT, anti-HBsAg antibody



## HIGH PREVALENCE CYTOMEGALOVIRUS REACTIVATION AND PREEMPTIVE TREATMENT FOLLOWING ALLOGENEIC STEM CELL TRANSPLANTATION AT BLOOD TRANSFUSION HEMATOLOGY HOSPITAL IN HO CHI MINH CITY

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**Purpose or Background:** Cytomegalovirus (CMV) reactivation at the time of impaired cellular immunity remains one of the important causes of morbidity and mortality after allogeneic stem cell transplantation. This report describes some results we achieved and access the efficiency of preemptive therapy of CMV infection after allogeneic stem cell transplantation.

**Method or Case:** We retrospectively analyzed 69 patients. All patients were monitored weekly for CMV PCR assay until D100 post-transplant. After D100, CMV PCR will be pretested per 3-6 month or whenever the patient has symptom of CMV infection. Therapy with Ganciclovir 5mg/kg twice daily was started in the presence of over 1000 CMV-DNA copies/ml blood for 1-3 weeks. When viral load decreased, the dose was tapered to 5mg/kg once daily and continued till two consecutive results were negative.

**Results or Progress:** Between Jan 2011 and Mar 2018, 69 patients underwent transplant from HLA-matched sibling donors (n=58) and haploidentical related donors (n=11). ATG-containing conditioning regimens were used in 27.5% of transplants. All donors and recipients were both CMV seropositive. The cumulative incidence of CMV infection was 81.2%. CMV infection was diagnosed at a median of 29.9 days. Graft-versus-host disease (GvHD) and prolonged using Corticoid was associated with increased risk of CMV infection. 44, 7, 4, 3 and 1 patients had CMV reactivation in 1 time, 2 times, 3 times and 4 times, respectively. Preemptive therapy using Ganciclovir was well-tolerated in all of patients with few complications. No evidence of CMV diseases was found in our patients. Patients who developed CMV reactivation showed no disadvantage in overall survival.

**Conclusion or Discussion:** Vietnam has over 99% patients in high-risk groups of CMV reactivation. Therefore, preemptive therapy has become standard approach for CMV reactivation and has effectively reduced incidence of CMV diseases after allogeneic stem cell transplantation.

**Keywords:** allogeneic stem cell transplantation, Cytomegalovirus, preemptive

PE-044

## LOCAL PREVALENCE AND SURVIVAL OUTCOME OF BACTERIAL INFECTION WITHIN 100 DAYS POST ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: A SINGLE CENTRE EXPERIENCE

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**Purpose or Background:** Bacterial infection is a significant complication and an important contributor to the morbidity and mortality in allogeneic hematopoietic stem cell transplantation (AHSCT). This study aims to determine the local prevalence of bacterial infection in post AHSCT and its impact on survival outcome.

**Method or Case:** A total of 213 patients who had undergone allogeneic HSCT were studied retrospectively from year 1993-2018. Out of these 213 patients, those who had a febrile episode defined by IDSA as a temperature  $>38^{\circ}\text{C}$  while being neutropenic with absolute neutrophil count (ANC)  $\leq 500$  cells/microliter were included in this study. Each separate occurrence of febrile neutropenia (FN) per patient was defined as one episode. Other factors affecting survival outcomes were also studied.

**Results or Progress:** 160 (75.1%) patients had FN, however only 97 (60.6%) of them have evidence of bacterial infection. Gram positive (GP) accounted for 40 (36.7%) patients; Gram negative (GN) accounted for 26 (23.9%), while mixed cultures (GP + GN) accounted for 43 (39.5%) patients and 64 (58.7%) had  $>1$  infections. There was a total of 49 bacterial isolates, of which the frequencies in descending order are as follows: methicillin resistant coagulase negative Staphylococcus (MRCONS) (23.1%), Escherichia coli (7.8%), and others. 47.2% of these infections were catheter related, while the rest were from other sources. 100days overall survival rate (OS) of patients post AHSCT with FN was 83.8%, which was similar to the statistics published in other studies.

**Conclusion or Discussion:** This study showed that MRCONS is the leading infection, hence empirical vancomycin might be appropriate in these patients. Since the largest source of infection is catheter-related, it warrants a need to reassess our standards of catheter care and the adherence to antibiotic stewardship program. Based on our results, we recommend combination therapy to include aminoglycoside as a routine to ensure 100% coverage.

**Keywords:** Allogeneic Haematopoietic Stem Cell Transplantation, Bacterial Infection, Febrile Neutropenia

## ORAL POSACONAZOLE VS. INTRAVENOUS-ORAL ITRACONAZOLE IN PREVENTING INVASIVE FUNGAL DISEASES FOR PATIENTS WITH ACUTE LEUKEMIA: A RETROSPECTIVE STUDY

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**Purpose or Background:** Oral posaconazole is superior to the same formulation of fluconazole or itraconazole in preventing invasive fungal diseases (IFDs) for patients with hematological malignancies; we previously found that sequential administration of intravenous and oral itraconazole was superior to oral itraconazole; however, there have been no reports about the comparison of oral posaconazole and itraconazole in sequential regimen.

**Method or Case:** This single-center, retrospective study enrolled patients with acute leukemia (AL). Prophylaxis with oral posaconazole or intravenous-oral itraconazole (intravenous formulation×2 day+oral suspension) was administered for patients recovering from neutropenia after chemotherapy.

**Results or Progress:** A total of 401 courses from 228 patients who received oral posaconazole (n=204) or itraconazole in sequential regimen (n=197) were recruited. Baseline characteristics in the two groups were not significantly different in terms of demographic data, underlying diseases, chemotherapy phases and neutropenia duration. The incidence of breakthrough IFDs was 0.0% (0/204) and 1.0% (2/197) in the posaconazole group and itraconazole group (P=0.241), while the incidence of proven, probable and possible IFDs was 5.4% (11/204) and 10.2% (20/197), respectively (P=0.074). The proportion of patients who needed systemic antifungal treatment were lower in posaconazole group than that in itraconazole group (5.9%vs.13.2%, P=0.012). Twelve cases (5.9%) experienced adverse events possibly associated with posaconazole and twenty-three cases (11.7%) with itraconazole (P=0.040). In clinical failure analysis, the failure rate of posaconazole group was lower as compared to the itraconazole group (5.9% vs. 13.7%, P=0.008). The acquisition costs of posaconazole were higher than those of itraconazole (P=0.000). There was no significant difference of the mortality between patients on posaconazole or itraconazole.

**Conclusion or Discussion:** Oral posaconazole and intravenous-oral itraconazole seems to have comparative clinical efficacy in the prevention of IFDs for AL patients. Oral posaconazole is safer and more tolerable while costs higher than intravenous-oral itraconazole.

**Keywords:** acute leukemia, neutropenia, invasive fungal diseases, posaconazole, itraconazole

PE-046

## SUCCESSFUL TREATMENT OF BK VIRUS HEMORRHAGIC CYSTITIS WITH LOW DOSE CIDOFOVIR AFTER MYELOABLATIVE ALLOGENIC HEMOPOIETIC CELL TRANSPLANTATION

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**Purpose or Background:** BK virus (BKV) hemorrhagic cystitis (HC) continue to be a serious cause of morbidity and mortality which complicates 5-40% of allogenic hemopoietic cell transplants. Supportive care including bladder irrigation and pain management remains the mainstay of therapy. Antiviral cidofovir has shown efficacy in the management of BK virus hemorrhagic cystitis.

**Method or Case:** Here we report outcome of two patients treated with low dose cidofovir at our centre.

**Results or Progress:** First patient is a 42 years old male, with Acute Myeloid Leukemia, t(6;9), post myeloablative (Bu-Cy conditioning with cyclosporine/methotrexate as GVHD prophylaxis), 10/10 matched sibling donor peripheral blood hemopoietic cell transplant in first complete Remission, developed severe dysuria and hematuria then urinary retention on day 35 transplant. urine BK virus came >60 million copies/ml while blood CMV, and BK Viruses were not detectable. He was treated with continuous bladder irrigation, PCA with morphine but did not benefit Then he was treated with Low dose cidofovir 1mg/kg/week along with intrabladder instillation with first dose. Rapid clinical and virologic improvement was seen and patient could be discharged home after third weekly dose of cidofovir without recurrence.

Second patient is a 22 years male with acute lymphoblastic leukemia, complex karyotype, post matched sibling Bu-cy peripheral blood hemopoietic cell transplant, developed severe hemorrhagic cystitis with urine BK virus load being >9 million copies on day +117 of transplant. He was treated with same protocol as above and complete response was achieved after 5 weeks of therapy.

**Conclusion or Discussion:** High clinical suspicion should be kept in patients who present with severe dysuria post allogenic transplant and urine sample should be sent for BK virus testing. Early administration of low dose cidofovir is required to reduce morbidity.

**Keywords:** BK virus, hemorrhagic cystitis

## THE EFFECT OF CONTINUOUS SCREENING OF CARBAPENEM-RESISTANT ENTEROBACTERIACEAE ON THE PREVENTION AND CONTROL OF BLOODSTREAM INFECTIONS IN PATIENTS WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Purpose or Background:** The aim of this study was to explore the effect of active carbapenem-resistant Enterobacteriaceae (CRE) screening combined with intervention measures on the prevention of bloodstream infections (BSIs) in patients with hematopoietic stem cell transplantation (HSCT) at the early stage of transplantation.

**Method or Case:** Patients underwent HSCT from September 1, 2017, to June 30, 2018, and from July 1, 2018, to February 28, 2019, were assigned as the single screening group and continuous screening group, respectively; patients transplanted from January 1, 2016, to August 31, 2017, and did not receive the active screening were assigned as the control group.

**Results or Progress:** Continuous CRE screening significantly improved the CRE gut detection rate compared with single screening (10% vs 1.5%,  $p=0.001$ ). The CRE infection rate in the pre-intervention period, single screening period and continuous screening period were 1.6%, 2% and 0, respectively. Related mortality was reduced in the single screening period and continuous screening period, being 50% and 0 compared with 66.7% in the pre-intervention period. *Escherichia coli* and *Klebsiella pneumoniae* were the main strains identified in CRE colonization (58.8%) and infection (80%) respectively. For CRE carriers during neutropenic fever, the time from detection to combination therapy including tigecycline ranged from -3 to 17 days. All CRE strains were resistant to expanded-spectrum cephalosporins penicillin/inhibitor combinations and ertapenem. The drugs with lowest resistance rates were tigecycline and amikacin, with 0% and 29.6% of the isolates being resistant to these agents, respectively.

**Conclusion or Discussion:** These results suggest that transplant patients have a high rate of gut colonization at the early stage of transplantation, and the implementation of regular continuous screening and control measures may effectively control CRE BSIs.

**Keywords:** hematopoietic stem cell transplantation, carbapenem-resistant Enterobacteriaceae (CRE), active screening, colonization

PE-048

## THE EFFICACY OF SURGERY COMBINED ANTIFUNGAL AGENT IN THE TREATMENT OF INVASIVE ASPERGILLOSIS OF OROFACIAL SOFT TISSUE IN A 9-YEAR-OLD GIRL WITH STEM CELL TRANSPLANTATION

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**Purpose or Background:** Aspergillus is recognized as being second to candidiasis that are affecting the paranasal sinuses and it leads to bone destruction and soft tissue necrotizing. Invasive aspergillosis frequently involves the lung and is uncommonly accompanied by soft tissue in highly immunocompromised patients after hematopoietic stem cell transplantation (HSCT). Especially, it is related to high mortality and morbidity.

**Method or Case:** We report a 9-year-old female patient who was diagnosed with acute myeloid leukemia (AML) in genetic presenting with AML1/ETO. Regarding induction failure with anthracycline and cytarabine, she underwent allogeneic HSCT myeloablative conditioning with busulfan/fludarabine from her haploidentical parents. The hepatic venous-occlusive disease developed on day 14 which is treated by defibrotide.

**Results or Progress:** Day 22 post-HSCT revealed a new right nasal cavity mucosal edema and orofacial soft tissue infiltration with aspergillus which is confirmed by endoscopy and histology result. After using a voriconazole agent with broad-spectrum antibiotics localized the infection and soft tissue necrotizing process. After three weeks for removing the infected tissue performed debridement with parotidectomy, maxillectomy surgery. A month after reconstruction operation with deltopectoral fascia-cutaneous is improved patient's condition. A CT scan revealed pericardial effusion and hepatic biopsy results the elevation of ferritin level confirmed hepatic hemosiderosis after 54 and 108 days, respectively. After the supportive care, condition of the patient was improved and she was discharged to home.

**Conclusion or Discussion:** Overall, only few cases of children with invasive aspergillosis of orofacial soft tissue after HSCT have been reported in the literature. Invasive aspergillosis of soft tissue is a severe complication affecting the outcome of HSCT which remains a considerable therapeutic challenge. Invasive aspergillosis of soft tissue can be treated with systemic antifungal agents primarily, but surgery can be considered an effective resort when the infection progresses despite medical treatment.

**Keywords:** Aspergillosis, hematopoietic stem cell transplantation, antifungal agent

## VIROLOGICAL MONITORING IN BONE MARROW TRANSPLANT(BMT) PATIENTS: EARLY DETECTION LEADS TO EARLY CONTROL OF DISEASE. RESULTS FROM A PEDIATRIC SUPER-SPECIALITY HOSPITAL IN INDIA

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**Background:** BMT involves the ablation of the host's haematopoietic and immune systems which makes the patient very susceptible to infections. The symptoms of viral infections are non-specific and hence routine monitoring for infections becomes important for early pick up. We report our centre's data on viral infections noticed in the post-transplant period and their effects.

**Method:** Data was prospectively collected and maintained for all patients who have undergone BMT at our institute from 10th August 2018 to 14th May 2019. A Cytomegalovirus(CMV), Adenovirus and Epstein Barr Virus(EBV) multi-virus Qualitative Polymerase chain reaction(PCR) panel and a BK virus qualitative PCR was sent to Igenetic lab in Mumbai, once every 2 weeks post engraftment. In addition,, samples were sent if the child presented with fever, rash, loose stools or hematuria. After Day 100, routine surveillance was stopped and tests ordered only if the patient was symptomatic.

The blood samples were sent in Ethylenediaminetetraacetic acid(EDTA) tubes and reported within 24 hrs. Quantitative PCRs were reported in 72 hrs.

**Results:** A total of 50 samples were sent from 17 patients during this period. Of these, 8 samples were positive for CMV, one for adenovirus and none for EBV. Quantitative PCRs for CMV were run for the positive samples and these were <1000 copies per ml for 5 samples and significantly increased in 3 (up to 1lakh copies/ml). The viremia cleared within 1 week of initiating Gancyclovir. BK viremia was not documented in any patient even though BK virus was positive in 2 of the 3 urine samples sent when the patients presented with hematuria.

**Conclusion:** Routine surveillance of post-transplant patients is a must and is recommended so that viral activation can be picked up early. Multiplex PCRs have the advantage of being a cost effective, fast and sensitive assay.

**Keywords:** monitoring, Cytomegalovirus, Epstein Barr Virus, Adeno virus, BK virus

PE-050

## A CASE OF MULTICENTRIC CASTLEMAN DISEASE WITH FAVORABLE OUTCOME BY RITUXIMAB MONOTHERAPY

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**Purpose or Background:** Castleman disease is an uncommon lymphoproliferative disorder characterized as either unicentric or multicentric. The clinical manifestation of multicentric Castleman disease (MCD) is various, not only multiple lymph nodes enlargement but also constitutional symptoms, skin lesion, endocrinopathy and organomegaly. We experienced one case of MCD with plasma cell variant which presented multiple lymphadenopathy mimicking lymphoid malignancy and treated the patient with Rituximab monotherapy successfully.

**Method or Case:** Sixty two year-old male who had been treated with insulin for diabetes mellitus complaint of multiple palpable mass at both neck and inguinal area. He did not have any symptom except lymph nodes enlargement. After visiting our hospital, CT scan was done and multiple lymphadenopathy was found at both neck, mediastinum and inguinal area. Excision biopsy was performed at neck lymph node and it showed MCD with plasma cell variant which expressed the immunohistochemical profiles with CD20(+); CD3(+); CD138(+); Kappa/Lambda(+); Bcl6(+); Ki-67(+); Bcl2(-); CD30(-).

**Results or Progress:** He was treated with Rituximab 375mg per body surface area weekly for 4 weeks without any serious complication. Compared with previous PET/CT scan, follow-up image after the completion of treatment showed markedly improvement with decreased lymph nodes' size and FDG uptake.

**Conclusion or Discussion:** We encountered the patient with MCD with plasma cell variant who was treated with Rituximab monotherapy showing favorable outcome. Continuous monitoring to detect relapse is required to this patient.

**Keywords:** Castleman disease, Rituximab



## A CASE OF STAGE IV NK/T-CELL LYMPHOMA IN THE BACKGROUND OF CHRONIC ACTIVE EPSTEIN-BARR VIRUS, TREATED WITH CHEMOTHERAPY, IRRADIATION, PEMBROLIZUMAB FOLLOWED BY TCR $\alpha\beta$ -DEPLETED HAPLOIDENTICAL TRANSPLANTATION

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**Background:** Natural killer (NK)/T-cell lymphoma is an aggressive malignancy of NK-cell origin. The role of haploidentical stem cell transplantation in advanced/refractory cases has not been elucidated.

**Case:** A 16-year-old boy with a skin lesion on his right upper arm was diagnosed with NK/T-cell lymphoma in the background of chronic active Epstein-Barr virus (EBV) via skin biopsy. Initial positron emission tomography-computed tomography (PET/CT) showed lymphoma involvement in multiple lymph nodes, both lungs, and right kidney. Blood EBV DNA viral load was  $8.27 \times 10^5$  copies/mL.

Despite one cycle of SMILE chemotherapy, PET/CT showed aggravated arm lesion and new hypermetabolic intra-abdominal nodes. For the second regimen, pediatric non-Hodgkin lymphoma protocol (Children's Cancer Group-1901) was started, but he developed persistent fever with hyperferritinemia. Bone marrow showed newly appeared lymphoma involvement and hemophagocytosis. Dexamethasone and etoposide were started, and pembrolizumab was administered for progressive lymphoma. Follow-up evaluations showed decreased activity of hemophagocytic lymphohistiocytosis with mixed lymphoma response. Gemcitabine, dexamethasone, and cisplatin (GDP) chemotherapy was initiated along with local radiotherapy on his arm. After 5 cycles of GDP, complete remission was verified in PET/CT and EBV viral load became negative.

Finally, he received ex vivo TCR $\alpha\beta$ -depleted haploidentical transplantation from his father. Conditioning consisted of low dose total body irradiation, anti-thymocyte globulin, fludarabine, and cyclophosphamide. The final infused graft contained  $3.18 \times 10^6$ /kg of CD34+ cells and  $2.25 \times 10^4$ /kg  $\alpha\beta$ + T cells. The engraftment of neutrophil and platelet was achieved without event on day 10 and day 17, respectively. There was no transplant-related complication, and full donor chimerism was sustained until 6 months after transplantation.

**Results:** The patient is alive without evidence of relapse for 6 months after transplantation.

**Conclusion:** We report a case of stage IV NK/T-cell lymphoma, who showed poor response to chemotherapy, but successfully achieved a sustained remission after chemo-irradiation with pembrolizumab followed by TCR $\alpha\beta$ -depleted haploidentical transplantation.

**Keywords:** NK/T-cell lymphoma, haploidentical stem cell transplantation, pembrolizumab, Epstein-Barr virus

PE-052

## CAPACITY BUILDING INITIATIVE TO IMPROVE DIAGNOSIS AND MANAGEMENT FOR LYMPHOMA IN DHAKA MEDICAL COLLEGE HOSPITAL (DMCH)

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**Purpose or Background:** The incidence of lymphoma is increasing all over the world both in western and Asian countries. A multicenter retrospective study had reported that NHL and HL comprises 16.9% and 3.9% respectively among the haematological malignancies over a 5 years study period in Bangladesh(1). The current problems in practicing lymphoma diagnosis in Bangladesh include relying more on morphology, scarcity of centers capable of immuno-histochemistry (IHC) and lack of potential clinical spectrum data of lymphoma. The purpose of this study is focusing capacity building in lymphoma management including importance of accurate diagnosis, management and post treatment follow up of lymphoma patients. We will also discuss the subtype distribution of lymphoma in DMCH, current strategies of treatment in this center and scope of research on improving the standard of management.

**Method or Case:** A retrospective analysis of histopathologic and immunohistochemistry profiles and clinical informations of different pattern of diagnosed 226 lymphoma cases at Hematology center DMCH, from January 2016 to December 2017.

**Results or Progress:** Out of total 226 lymphoma cases 160 patients were NHL and 66 were HL. The mean age of HL is 30 (range 4-60) years and of NHL is 43( 12-90) years. The M:F ratio is about 3:1. Finally 125 NHL patient's clinical parameters, histopathology, IHC and other investigations were evaluated. The most common variant was found aggressive DLBCL (60/48.38%), followed by PTCL 16(12.8%), very aggressive lymphoblastic lymphoma (LBL) 14(11.2%), low grade follicular lymphoma 14(11.2%) and others 21 ( 16.42%).

**Conclusion:** The NHL is a common hematologic malignancy worldwide including Bangladesh, but there is scarcity of national data representing incidence, subtype and clinical spectrum . Improving the infrastructure for accurate diagnosis of lymphoma, optimal patient management and ongoing training for physicians are key to meaningful translational research and scientific advances.

**Keywords:** DLBCL, NHL, PTCL, IHC, HL, LBL

## CHANGES OF RED BLOOD CELL PARAMETERS IN NON-HODGKIN LYMPHOMA

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**Purpose or Background:** Since 1990s The International Prognostic Score (IPI) is widely wielded to evaluate stage, risk and prognosis of lymphoma. Recent studies have demonstrated that increased red cell distribution width (RDW) is associated with late stage of disease, and mortality in various malignant and nonmalignant diseases. From these results we pointed that correlation between red cell parameters and IPI scoring may play important role in risk stratification of patients with non-Hodgkin lymphoma (NHL).

**Method or Case:** Diagnose of 62 newly diagnosed patients with NHL from January 2018 to January 2019 at the Center of Hematology and BMT of First Central Hospital was proved by immunohistochemistry. From them this study was conducted 30 patients, for whom were able to do final evaluation after all cycle chemotherapy. Risk factors of disease were evaluated by IPI scoring system. Complete blood count was analyzed by automated analyzer Sysmex XH 2000. Kaplan-Meier survival analysis was used to examine the effect of RDW on overall and disease free survival. STATA12 software was used for statistical analysis.

**Results or Progress:** The median age of participants is  $50.13 \pm 15.36$  years (range 17-81). Overall 60% (18) of patients were males. 37% (11) of them were from Ulaanbaatar, 63% (19) from the rural area of Mongolia. By immunohistochemistry, B cell lymphoma is dominated among cases of NHL (83%). The occurrence of "B" syndrome was noticed in 53.3% (16) of patients at the time of diagnosis. The IPI score showed 6.67% of patients were in low risk, 33.33% in low-intermediate risk, 36.76% in intermediate-high risk and 23.33% in high risk. Adverse prognostic factors were presented as follows: 5 (16%) of them were age more than 60 years old, LDH was measured higher than normal in 11 (36.6%) cases ( $p=0.009$ ). Clinical assessment showed that 27 (90%) cases were in advanced Ann Arbor stages at the time of diagnosis. According to Zubrod scoring system the performance status of patients were evaluated by two points and above. A total of 12 patients (40%) had more than two extra nodal organ involvement. Hemoglobin was  $126.5 \pm 85$  g/l, red blood cell  $4.4 \pm 3.7 \times 10^{12}/l$ , MCV  $85.3 \pm 34$  fl, MCH  $28.7 \pm 14.1$  pg, MCHC  $33.2 \pm 6.9$  g/dl. 11 patients (36.6%) had various stage anemia. From them in 3 case (27%) revealed microcytic, hypochromic anemia. RDW was  $15.36 \pm 3.15\%$ , whereas PLR was  $268.936 \pm 200.96$ . Elevated RDW at the diagnoses was negatively correlated with overall survival ( $p=0.03$ ), but not to treatment outcomes ( $p=0.07$ ). There is no statistical significance difference between RDW's level in disease free survival ( $p=0.5$ ).

**Conclusion or Discussion:** Results above suggested that B cell lymphoma is dominated among NHL cases and

most of them is diagnosed in late stages. IPI scoring including increased LDH level, late staging by Ann Arbor, more than two extra nodal organ involvement is more significant in our cases. High RDW at the diagnoses is associated with mortality.

**Keywords:** : Non-Hodgkin Lymphoma, IPI scoring, Red cell distribution width (RDW)

PE-054

## CLINICAL ASSOCIATION OF HIGH-MOBILITY GROUP PROTEIN B1 (HMGB1) WITH ACUTE GRAFT-VERSUS-HOST DISEASE AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN NON-HODGKIN LYMPHOMA

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**Purpose or Background:** Several studies have demonstrated that various cytokines can modulate the immune reactions after allogeneic hematopoietic stem cell transplantation (HSCT). Among them, High mobility group box 1 protein (HMGB1) is a pleiotropic cytokine that functions as a pro-inflammatory signal, important for the activation of antigen presenting cells (APCs) and propagation of inflammation. HMGB1 is implicated in the pathophysiology of a variety of inflammatory diseases, and we have recently found the variation in the HMGB1 gene to be associated with mortality in patients with systemic inflammatory response syndrome. Since acute graft-versus-host disease (aGVHD) is a similar pathophysiology, the aim of this study is to investigate the relationship between serum HMGB1 and aGVHD.

**Method or Case:** The blood samples and tissue samples were analyzed for cytokines of damage-associated molecular pattern including of HMGB1 for following groups: healthy controls, patients treated with chemotherapy alone, autologous HSCT recipients, an allogeneic HSCT as well as aGVHD patients after HSCT.

**Results or Progress:** The serum HMGB1 levels were highly increased in aGVHD group (35.92 ng/mL,  $p=0.0003$ ) compared to control group. And it was identified that HMGB1 was not increased by conventional chemotherapy (median 3.56 ng/mL, 1.59 ng/mL at pre- and post-chemotherapy) and healthy status (median 4.06 ng/mL). Also, it was found that even aGVHD patients would decrease again after aGVHD was treated (median 18.34 mng/mL,  $p<0.001$ ). In order to assess whether increased HMGB1 level is caused the tissue damage by conditioning chemotherapy itself during HSCT, serum HMGB1 level was examined in group receiving autologous or allogeneic HSCT for serial period, compared to aGVHD group. The serum HMGB1 levels in the active aGVHD was significantly higher than those in any period during auto-HSCT or allo-HSCT ( $p=0.0018$ ). Also, HMGB1 level in patients with a higher aGVHD grade tended to be greater than those in patients with a lower aGVHD grade.

**Conclusion or Discussion:** This study suggest that HMGB1 may be a useful marker of aGVHD and it is not related to chemotherapy alone or autologous HSCT. Also, Targeting HMGB1 protein production or release might have potential therapeutic approach for aGVHD.

**Keywords:** HMGB1, acute GVHD, allogeneic HSCT, lymphoma, cytokine, biomarker

PE-055

## CLINICAL IMPLICATION OF EX VIVO PURGING WITH CLINIMACS CD34(+) CELL SELECTION IN AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR T-CELL LYMPHOMAS

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**Purpose or Background:** Although autologous hematopoietic stem cell transplantation (auto-HSCT) is one of the best curative strategies for patients with chemosensitive T-cell lymphoma, major limitation remains a tumor contaminated graft-related relapse or residual disease after chemotherapy. To improve these limitations, several purging methods were introduced in auto-HSCT. However, there are few studies of ex vivo purging of the autograft in lymphomas, especially T-cell lymphoma. Therefore, to confirm the efficacy of ex vivo purged autograft, we retrospectively analyzed 59 consecutive patients diagnosed with T-cell type non-Hodgkin lymphoma who receiving auto-HSCT with/without ex vivo purging.

**Method or Case:** Among them, 33 patients underwent autograft manipulation with ex vivo purging by CD34+ cells selection using a CliniMACS device.

**Results or Progress:** With median follow-up duration of 42 months (range, 6-121 months), 3-year overall survival (OS; 73.8% vs. 49.0%,  $p=0.017$ ) and 3-year progression-free survival (PFS; 75.8% vs. 52.4%,  $p=0.039$ ) in a purged and unpurged group, respectively. Transplant-related mortality was observed in both groups (2 patients of a purged group and 1 patient of an unpurged group). Neutrophil (10 vs. 9 days,  $p=0.240$ ) and platelet (30 vs. 24 days,  $p=0.055$ ) recovery were similar in both group and there was no engraftment failure. On subgroup analysis according to upfront and salvage auto-HSCT, while survival outcomes were improved by stem cell purging in the upfront auto-HSCT (OS with  $p=0.039$  and PFS with  $p=0.047$ ), there were no different survival outcomes in salvage auto-HSCT.

**Conclusion or Discussion:** Although cohort was a small number, ex vivo graft-purging method was feasible and safe in T-cell lymphomas. And this purging strategy observed the more favorable survival outcomes in the upfront auto-HSCT than salvage setting. Therefore, further randomized studies are needed to determine the firm efficacy of CD34+ purification with the large number of patients in auto-HSCT for T cell-lymphomas.

**Keywords:** ex vivo purging, CliniMACS, T-cell lymphoma, autologous stem cell transplantation, clinical significance

PE-056

## EFFECTIVENESS AND INFECTIOUS COMPLICATIONS IN PATIENTS WITH LYMPHOMA USING HIGH-DOSE RITUXIMAB CONDITIONING REGIMEN DURING AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Background:** The application of rituximab during auto-HSCT plays an important part in eliminate of residual disease and in vivo purging. The majority of studies used standard-dose rituximab (R-BEAM; 375mg/m<sup>2</sup>) treating lymphomas during auto-HSCT. We investigated impact of high-dose rituximab (HR-BEAM; 1000mg/m<sup>2</sup>) on infections and immune reconstitution during auto-HSCT.

**Material and Methods:** We reviewed 104 patients with relapsed or refractory aggressive B-cell Non-Hodgkin lymphomas (NHL) who received different doses of rituximab during auto-HSCT. Divide into groups: HR-BEAM (N=34); R-BEAM (N=30); BEAM (N=40). Immune reconstruction, occurrence rate and pathogens distribution of infections, and treatment and outcome of patients were detected and recorded. The factors related to infections following auto-HSCT were analyzed retrospectively.

**Results:** The OS at 3 years was 67.8% for HR-BEAM, 58.7% for R-BEAM and 48% for BEAM (P =0.04). DFS was 64.5% for HR-BEAM, 55.8% for R-BEAM and 44% for BEAM (P = 0.03). 88 patients (84.62%) developed infections with no death at early stage after auto-HSCT. There was no significant difference in bacterial infection within 3 months after auto-HSCT. A total of 11 cases fungal were isolated, including 4 strains from HR-BEAM, 5 strains from R-BEAM and 2 strains from BEAM. The rate of viral infection was 14.47% for HR-BEAM, 10.00% for R-BEAM and 5.00% for BEAM (P = 0.24). The percentage of IgG after six months of the auto-HSCT compared with those at diagnosis was 19.29% for HR-BEAM, 50.1% for R-BEAM and 49.88% for BEAM. There was no significant difference in immunoglobulin recovery and B-cell recovery among three groups after 2 years of transplantation.

**Conclusions:** Using HR-BEAM during auto-HSCT is a feasible and promising treatment for relapsed or refractory aggressive B-cell NHL and has better effectiveness and controllable infectious complications. When hypogammaglobulinemia and B-cell alymphocytosis occure within 3 months after auto-HSCT, intravenous immunoglobulin can reduce infection.

**Keywords:** Lymphoma, Autologous Hematopoietic Stem Cell Transplantation, High-Dose Rituximab, Immune Reconstruction, Infectious Complications



## FOLLICULAR LYMPHOMA PRESENTING WITH MONOCLONAL IGM AND MYD88 MUTATION: A CASE REPORT AND REVIEW OF THE LITERATURE

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**Introduction:** Follicular lymphoma (FL) is an indolent lymphoproliferative disorder of B-cells, accounting for 3.2~7.0% of non-Hodgkin lymphoma in China. MYD88 is an important adaptor protein in the nuclear factor- $\kappa$ B and mitogen-activated protein kinases signaling pathways. The somatic mutation of MYD88 has been reported in different types of hematological malignancies. However, the mutation has not been reported in primary FL. We described a newly diagnosed FL patient with MYD88 L265P mutation and immunoglobulin (Ig) M monoclonal gammopathy.

**Case Report:** A 62-year-old male developed a painless mass under the right jaw in 2017, in which the mass enlarged gradually. He underwent a PET-CT scan showed systemic swollen lymph nodes which indicated a diagnosis of lymphoma. The pathological report of the right submandibular mass revealed that small atypical lymphocytes diffusely or follicle-like distributed. The absolute number of centroblasts was 0-5 for each high-power field. Immunohistochemistry stain showed that the tumor cells were positively associated with CD20, CD CD79 $\alpha$ , CD43, CD10, and Bcl-2, and negatively associated with CD3, CD5, Bcl-6, and Cycline-D1. The pathological diagnosis was follicular lymphoma, grade I. A bone marrow invasion of lymphoma cells was confirmed by bone marrow aspiration and flow cytometry. The patient was eventually diagnosed with follicular lymphoma (grade 1, stage IV). Given the repeated unexplained fever and night sweating, he received 4 cycles of modified R-CHOP (rituximab (600 mg d0), cyclophosphamide (1.0 g d1), Pegylated liposomal doxorubicin (20 mg d1), vincristine (4 mg d1), and prednisone (90 mg d1-d5)). After 4 cycles of modified R-CHOP, his symptoms disappeared. But the interim PET-CT scan indicated a stable disease. Given the abnormal elevation of IgM serum concentration both before and after R-CHOP, a serum immunofixation test was performed and showed the existence of monoclonal IgM and lambda light chain in the blood. A MYD88 L265P somatic mutation was confirmed by polymerase chain reaction. An alternative regimen, involving bortezomib (rituximab (600 mg d1), bortezomib (2.3 mg d1, 8, 15), dexamethasone (20 mg d1, 8, 15)) was presented. After 2 cycles of R-Vd regimen, serum IgM concentration significantly decreased. The patient also received continuous R-Vd regimen and waited for another PET-CT scan.

**Conclusion:** We describe a case of FL with MYD88 L265P mutation who poorly responded to immunochemotherapy. Bortezomib may benefit these patients.

**Keywords:** follicular lymphoma, monoclonal gammopathy, immunochemotherapy, MYD88 mutation

## INCIDENCES OF HBV AND HCV INFECTIONS AMONG ADULTS WITH NON-HODGKIN LYMPHOMA COMPARED WITH AMONG BLOOD DONORS

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**Purpose or Background:** It has been documented that hepatitis B virus (HBV) and hepatitis C virus (HCV) are primarily hepatotropic and also lymphotropic. Moreover, these viruses may have some involvement with the development of lymphatic disorders, such as Non-Hodgkin's Lymphoma (NHL). The incidence of lymphoma around the world has increased since 2000, especially B-NHL which accounts 80-85% of all Lymphoma. It has also been observed that the incidence of Lymphoma in Mongolia is increasing in the last 5 years. Therefore, it is interesting to study, incidences of HBV and HCV among lymphoma patients and to determine incidences of HBV and HCV among patients diagnosed with B-cell non-Hodgkin Lymphoma and compare it with the prevalence of donor group in Mongolia.

**Method or Case:** A retrospective and prospective study were carried out reviewing records of 232 patients with lymphoma admitted between 2015-2018 in a single center of Mongolia. Lymphoma was diagnosed by immunohistochemistry and laboratory test.

**Results or Progress:** Overall, a total of 232 patients were enrolled in the study including 110 (47.7%) male and 122 (52.6%) female; average age was  $54.3 \pm 15.6$ . 112 (48.3%) of them were from the countryside, while 120 (51.7%) were from urban areas. Incidences of B-NHL per 100,000 population among 20-39, 40-59, 60-69 and  $\geq 70$  years old male group were 0.74-0.93, 2.92-4.41, 9.3-12.01 and 10.73-17.59, respectively, while it was 1.1-1.29, 2.8-3.75, 8.02-16.25 and 10.77-17.72, respectively for female group. Among B-NHL patients, 123 (53%) patients were diagnosed with HBV or HCV and 3 (1.3%) were coinfecting with HBV and HCV. Furthermore, the prevalence of HBV and HCV among blood donors who are 20-39 years old, were 3.0% and 2.0%, respectively, while it was 4% and 6.8% between 40-59 years old. In addition, incidences of HBV and HCV among patients with B-NHL was significantly higher compared to the prevalence of blood donors ( $p < 0.01$ ).

**Conclusion or Discussion:** The current study shows that incidence of B-NHL is directly related to the age of patients. It also demonstrates that incidence of anti-HCV and HBsAg among B-NHL patients is significantly higher than that of anti-HCV and HBsAg among donors. Furthermore, incidences of B-NHL per 100 000 population is tended to be increasing, especially among elderly man.

**Keywords:** hepatitis B virus, hepatitis C virus, Non-Hodgkin's Lymphoma, immunohistochemistry

## METRONOMICS - POSSIBLE CLINICAL APPLICATION IN POST AUTOLOGOUS STEM CELL TRANSPLANT RELAPSE FOR LYMPHOMA

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**Background:** naplastic diffuse B-Cell lymphoma (A-DLBCL) a rare morphological entity remains an inexplicable disease due to its heterogeneous clinicopathological distinctiveness. Role of metronomic in post autologous stem cell transplant (ASCT) relapse not amenable to subsequent allogenic transplant is justified. We report a case of A-DLBCL post-transplant relapse achieving durable complete response (CR) with metronomic therapy.

**Case:** 58 years, male diagnosed as a case of A-DLBCL in July 2011, had partial response (PR) after first line chemotherapy with 6 cycles of CHOP. Patient had disease progression in June 2012, received GemOX chemotherapy, had PR but refused for transplant. Patient had subsequent progression in January 2013, received R-ICE salvage chemotherapy, was in PR, followed by high dose chemotherapy (HDCT) with CBV and ASCT in July 2013. Post ASCT in CR, till January 2014. Upon subsequent relapse after 8 months post ASCT, patient refused for allogenic transplant and was started on single-agent vinblastine metronomic therapy 6mg/m<sup>2</sup>/week. With modification in dose and interval (Vinblastine at 75% from 13th dose and every biweekly from 20th dose onwards), patient received total of 92 doses till December 2017 with a documented good partial response after 15 doses. Upon further histologic proven progression in February 2018, second line metronomic therapy was started with combination of prednisone, etoposide, procarbazine and cyclophosphamide (PEP-C); 3 weeks on, one week off every 28 days. Patient received 12 months of PEP-C with some dose modification for toxicities, till February 2019 and attained a metabolic CR, is now on follow-up

**Discussion:** A-DLBCL has aggressive clinical course and patients have worse outcome even with ASCT. Angiogenesis plays important role in pathophysiology and prognosis of aggressive lymphoma. Endothelial cells are highly and selectively sensitive to very low doses of various chemotherapeutic drugs (Vinblastine, PEP-C). Our case is first reported case of two lines of metronomic for longest duration post-transplant relapse.

**Keywords:** Metronomic, Lymphoma, Relapse, Transplant, Chemotherapy, Progression

PE-061

## THE EFFECT OF UPFRONT AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA: A MULTICENTER RETROSPECTIVE STUDY

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**Purpose or Background:** It is still controversial that upfront autologous stem cell transplantation (ASCT) improves the survival rate in patient with diffuse large B cell lymphoma (DLBCL).

**Method or Case:** We retrospectively analyzed patients who were diagnosed with DLBCL and treated with CHOP based chemotherapy, and aged from 18 to 64 at the time of diagnosis in two institutions between January 1998 and August 2018.

**Results or Progress:** A total of 250 patients were included. Forty-two patients underwent upfront ASCT and 208 patients underwent only chemotherapy. Rituximab was administered to 182 patients, 36 in ASCT group and 146 of chemotherapy-only group. In the analysis of overall patients, the use of Rituximab improved relapse free survival (RFS) (19.8% vs. 32.4%,  $p=0.044$ ) and progression free survival (PFS) (31.3% vs. 51.5%,  $p=0.003$ ) compared non-rituximab chemotherapy. Low International Prognostic Index (IPI) improved PFS ( $p=0.022$ ) but not RFS (0.897). Upfront ASCT did not show any improvement in RFS compared to chemotherapy-only (26.2% vs. 22.6%, respectively;  $p=0.689$ ) or PFS (36.8% vs. 37.5%, respectively;  $p=0.726$ ). In a subgroup analysis that received Rituximab, upfront ASCT also did not improve RFS compared to chemotherapy-only (25.0% vs. 18.5%, respectively;  $p=0.254$ ) or PFS (30.6% vs. 31.5%, respectively;  $p=0.542$ ). In the analysis according to IPI, upfront ASCT did not improve RFS and PFS.

**Conclusion or Discussion:** IPI is still a strong, independent prognostic factor. Upfront ASCT did not improve RFS or PFS, the studies of large number of high-risk patients are needed

**Keywords:** DLBCL, upfront autologous stem cell transplantation

## COSTS OF AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS OF MULTIPLE MYELOMA IN STATE-SPONSORED HEALTH CARE UNIT FROM INDIA

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**Purpose or Background:** Autologous Haematopoietic Stem Cell Transplantation (ASCT) has been an integral part of the management of Multiple Myeloma (MM) patients. Cost plays a major role in the therapeutic decision making in resource constraint settings. The cost of transplant in state-sponsored health care units has not been studied to date.

**Method or Case:** Forty patients of MM who underwent ASCT were prospectively included in this study. The costs were divided into fixed costs (constant and mandatory for all patients undergoing ASCT) and variable costs (specific to each patient). The cost of drugs was based on the last purchase price (LPP) by the hospital. All costs were calculated in INR. Statistical analysis was done using R and JMP ver 13.1.0.

**Results or Progress:** The fixed cost for the ASCT was INR22,834/-. The mean variable cost was INR68,421 ( $\pm 35,353$ , 23,038-195,370). The mean total cost was INR91,263 ( $\pm 35,353$ , 45,872-218,204). These costs were much cheaper than the previous analysis done at another government institute (INR500,631) where the patients pay for their own expenses (Malhotra et al, 2007). The fixed cost constituted 25% of the total costs. Of the variable costs, the maximum expenditure was for plerixafor (13.1%), followed by antibiotics (12.3%), and antifungals (14.2%). While each additional day of BMT stays cost the exchequer INR1,997/-, BMT stays itself was not significantly associated with the total cost ( $r=0.4$ ,  $p=0.106$ ). There was a moderate correlation of the patients' antibiotic requirement and total cost ( $r=0.65$ ,  $p=0.001$ ) that was statistically significant, suggesting a major role of infection in the transplant costs.

**Conclusion or Discussion:** The results signify that all eligible patients should be offered transplant in our settings as the total cost to the Exchequer (State) is significantly lower. The cost from the societal perspective was not considered in this study, which should be studied in the future.

**Keywords:** Cost Analysis, Autologous Transplantation, Myeloma, State sponsored

PE-063

## DETERMINANT FACTORS FOR EARLY MORTALITY IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS

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**Purpose or Background:** In the recent years we have observed a great improvement in the survival of patients with multiple myeloma (MM), because of the novel treatments and drugs. But the challenge still remains for the survival of about 10% of MM patients who die very fast after the disease diagnosis. In this study we try to investigate the associated factors for early mortality in MM patients.

**Method or Case:** We evaluated 315 newly diagnosed MM patients from the registry of Alzahra Hospital between 2006 and 2017. Early mortality (within 2 month of diagnosis) were detected among those patients and disease history and baseline characteristics and laboratory data were used in univariate and multivariate analysis to find the independent factors which are associated with the early mortality.

**Results or Progress:** Thirty six patients (11.4%) experienced early mortality. In the univariate analysis male gender, Hemoglobin less than 10 g/dL, platelet less than 150,000/ $\mu$ , serum albumin less than 3.5 g/dL, corrected serum calcium more than 12 mg/dL, serum creatinine more than 2 mg/dL, lactate dehydrogenase (LDH) more than 250 U/L and serum beta 2 microglobulin more than 5500 md/L were associated with early mortality (all p values less than 0.05). Multivariate analysis showed that male gender (OR= 3.2, CI=2.8-4.9), having the serum albumin less than 3.5 g/dL (OR= 2.2 CI=1.5-6.1), corrected serum calcium more than 12 mg/dL (OR=1.3, CI=1.1-3.6), LDH more than 250 U/L (OR=1.7, CI=1.3-5.2) had independent effects on the early mortality when controlling for other risk factors.

**Conclusion or Discussion:** We can conclude that male MM patients with serum albumin less than 3.5 g/dL, corrected serum calcium more than 12 mg/dL and LDH more than 250 U/L have a greater risk for the early mortality.

**Keywords:** Multiple Myeloma, mortality, serum albumin level, lactate dehydrogenase

## EFFICACY AND SAFETY OF CARFILZOMIB BASED TRIPLET THERAPY FOR ELDERLY MULTIPLE MYELOMA PATIENTS: A SINGLE CENTER EXPERIENCE

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**Background:** For autologous stem cell transplantation (ASCT) eligible multiple myeloma (MM) patients, there is little concern about choosing carfilzomib-based triplet therapy as second line treatment. On the other hand, for ASCT ineligible patients the decision is more complicated. Although we have learned from the ASPIRE trial that KRd (carfilzomib, lenalidomide, dexamethasone) is superior to Rd (lenalidomide, dexamethasone) regardless of age, how readily these results can be implemented to our real-world practice is a different matter because trials usually exclude the more frail patients and Asian patients tend to be less tolerable to chemotherapy to begin with. To evaluate the safety and efficacy of KRd compared to Rd in real-world practice, we carried out this study.

**Method:** This was a single center, retrospective, longitudinal cohort study. We compared the outcomes of MM patients  $\geq 65$  years old who received either Rd (N=26) or KRd (N=14) as second line treatment after VMP (bortezomib, melphalan, prednisone) since January 2016. We collected and analyzed clinical and survival data of the enrolled patients.

**Results:** There were no differences in baseline characteristics between the 2 groups. During the median follow-up of 35 months, the median progression free survival (PFS) was 10 months for both Rd and KRd groups ( $P=0.905$ ). When the best response was considered, the proportion of patients showing very good partial response (VGPR) or better response was slightly higher in KRd group (38.5%) compared to Rd group (34.6%). If partial response (PR) was used as the cutoff, the difference became more prominent (78.6% for KRd vs. 73.1% for Rd). Only 1 patient from KRd group had a significant cardiac adverse event in the form of heart failure but the patient recovered without sequelae.

**Conclusion:** KRd seems to be an effective and safe option for elderly Asian patients with relapsed MM.

**Keywords:** carfilzomib, multiple myeloma, elderly patients

## MEDICAL RESOURCE CONSUMPTION ANALYSIS OF AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN MULTIPLE MYELOMA PATIENTS

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**Background:** Multiple myeloma, a form of hematologic malignancy, is characterized by abnormal proliferation of plasma cells in the bone marrow. This disease is refractory to treatment and tends to occur in elderly people. Once the disease develops, huge amounts of medical resources are consumed. Hematopoietic stem cell transplantation is currently the most effective treatment method. We conducted a medical resource consumption analysis in multiple myeloma patients who received hematopoietic stem cell transplantation at a single center and studied the 30-day readmission rate, number of outpatient visits, number of hospitalizations, number of emergency department visits, total outpatient costs, total length of hospitalization, and total cost of hospitalization of these patients.

**Method:** This was a retrospective study, and the subjects were newly diagnosed multiple myeloma patients who received hematopoietic stem cell transplantation from January 2010 to 31 December 2017 at a single medical center.

### Statistical analysis methods

1. Descriptive statistic
2. Inferential statistics

**Results:** A total of 140 patients were included in the study; of these, 26 underwent hematopoietic stem cell transplantation. The mean age of patients who received hematopoietic stem cell transplantation was  $57.77 \pm 8.24$  years. The mean number of outpatient visits was  $97.77 \pm 64.72$ , mean number of hospitalizations was  $5 \pm 3.09$ , mean number of emergency department visits was  $3.04 \pm 5.02$ , total outpatient cost was  $1,318,724.23 \pm 1,009,450.62$  NTD, and total hospitalization cost was  $1,020,685.5 \pm 478,821.88$  NTD.

**Discussion:** Hematopoietic stem cell transplantation is one of the most effective treatment methods for multiple myeloma. However, whether these patients can undergo transplantation is determined largely by their physical status and age. The study results can provide a reference for health authorities to formulate payment criteria for various diseases in the future, which may result in effective utilization of medical resources and improvement in healthcare quality.

**Keywords:** multiple myeloma, medical resource consumption, autologous hematopoietic stem cell transplantation



## PATTERN OF PRESENTATIONS IN PLASMA CELL LEUKEMIA IN INDIA

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**Purpose or Background:** Plasma cell leukemia (PCL) is a rare disorder with poor prognosis.

**Method or Case:** Ten cases were retrieved (5 males & 5 females)

**Results or Progress:** All the cases except one were primary. The median duration between appearance of symptoms & diagnosis was approximately 3-4 months. All presented with typical features of multiple myeloma (MM) e.g. low back pain, bony lesions & renal failure.

Some had fever, cough with pleural effusion and progressive fatigability limiting mobility. All showed M-band positive in both serum & urine on electrophoresis except one, which showed negative in serum but positive in urine. The case with pleural effusion showed M band in pleural fluid too. This case showed hepatosplenomegaly too. One case relapsed after approximately two & half year of initial diagnosis, and is on follow up till date (2 years after relapse).

On immunofixation five showed IgG kappa, one showed IgG lambda, kappa & lambda light chain each & the last one showed high Kappa at initial diagnosis followed by relapse (after approximately two & half year of initial diagnosis) with IgG kappa type – a lineage shift; a rare event.

HCT was done in one case for PCL. In 2nd case HCT was done for MM; was diagnosed as PCL 4.5 years after MM diagnosis. Three cases underwent flowcytometry, showed CD 38 & CD138 positive and CD 19 & CD56 negative. CD45 showed variable expression. All treated with PAD (Bortezomib, Doxorubicin & Dexamethasone) regimen. Overall survival: Out of 9 cases, 4 are alive, 2 died after 3 months one after 4, 7 & 22 months each after diagnosis.

**Conclusion or Discussion:** It is relatively easy to diagnose by simple routine investigations e.g. hemogram, B.M. Aspirate, serum/ urine electrophoresis, x-ray etc. early diagnosis will help in better outcome.

**Keywords:** Plasma cell leukemia, Myeloma, Immunophenotype

## TREATMENT RESPONSE IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS

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**Background:** Multiple myeloma (MM) is a malignancy of plasma cells that commonly results in overproduction of monoclonal immunoglobulins. Important advances in the management of this disease have resulted in higher rates of remission and improved overall survival. Although its treatment outcomes have improved but relapse remains a serious problem. The aim of the study was to compare and evaluate treatment response in newly diagnosed Multiple Myeloma patients.

**Method:** A Prospective, observational study was conducted from January 2015 to June 2018 at NIBD on newly diagnosed MM patients. Remission was documented after 4 cycles of treatment according to the standard response criteria of International Myeloma working group (IMWG).

**Results:** Total of 90 patients were included in the study of which 50(55.5%) were male and 40(44.4%) were female. Patients were classified into stage I (44%), stage II (30%) and stage III (16%) according to the new international staging system. Screening tests showed Del17p53 positive in 3.3%, monoclonal gamopathy in 94.3% patients during the initial period of chemotherapy. Imaging studies showed lytic lesion in 30% patients. Bone marrow plasma cells 10-20% in 15.6% and >20% in 78.9% patients. Induction regimen used includes LENA/DEXA/BORT, THAL/DEXA/BORT, DEXA/BORT/CYCLO, THAL/DEXA/CYCLO. Best response was achieved by LENA/DEXA/BORT group (34.45%).

Out of 90 patients 15(18.5%) patients were found to be transplant eligible who were consolidated using high dose Melphalan. However transplant ineligible patients were continued to maintenance therapy after induction period. Hence survival rate of transplant eligible patients was 86.6%, whereas survival rate of transplant ineligible patients was 72%.

**Conclusion:** Treatment with LENA/DEXA/BORT combination was superior to the thalidomide group. Survival rate of transplant eligible patients was observed to be more pronounced than the ineligible patients. Although there is virtually no cure with current therapies, the survival benefit is meaningful for patients with responsive disease.

**Keywords:** Multiple Myeloma, Induction, Transplant, Maintenance therapy, Consolidation

## APPROACH OF APPEARANCE CARE FOR PATIENTS WHO UNDERGO HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Background:** Changes in appearance for patients who undergo hematopoietic stem cell transplantation (HSCT) are serious problems in both women and men. Alopecia due to conditioning regimens consisting of chemotherapy and total-body irradiation is one of them even after discharge. Furthermore, chronic graft-versus-host disease usually causes appearance problems such as skin rash, dry skin, pigmentation, and nail atrophy. Worrying about other people noticing, they become reluctant to go out, leading to delays in social rehabilitation. Herein, we will introduce our approach to these appearance problems after undergoing HSCT.

**Activities:** We provide a support program for appearance care as advanced information. We introduce patients who undergo HSCT to appearance care goods, such as medical wigs and cosmetics, as well as symptom management by the multidisciplinary team for appearance care.

Positive opinions after the support program by participants were as follows: "It was useful to know the concrete way of handling appearance change," "I was relieved to know that I was not the only one who had fear for appearance changes," and "It was valuable to hear about cancer patients' actual experiences."

In an interview by long-term follow-up (LTFU) nurses, we considered what we can do for patients who undergo HSCT in order to "live in society," "live as an individual person," manage the symptoms, build closeness, and accept their feelings.

**Conclusion:** We are providing appearance care for the purpose of "living in society after HSCT." It is important that patients who undergo HSCT have opportunities to obtain correct information on appearance care from LTFU nurses and appearance care multidisciplinary teams easily, leading to relief and help for patients' better lives.

**Keywords:** APPEARANCE CARE, LTFU

## CHEMICAL SUBSTANCES IDENTIFICATION OF "GABUS FISH" (CHANNA STRIATA), A TRADITIONAL DRUG USED BY MANDAR PEOPLE TO ACCELERATE THE HEALING OF INJURY AFTER SURGERY

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**Purpose or Background:** A "Gabus fish" (Channa Striata) is one type of freshwater fish that is widely used by the community to heal injury, especially injury after surgery. The aims of the research was study a chemical substance identification of "Gabus fish" (Channa Striata), one of traditional drug used by Mandar people to accelerate the healing of injury after surgery.

**Method or Case:** Method used in this research was meta-analysis. Data were collected by interviews and observations in Mandar people (One of ethnic in West Sulawesi) who lives in the Lena area, Campalagian district, Polewali Mandar, West Sulawesi, Indonesia. In addition, have been done literary studies on chemical substances contained by "Gabus fish" (Channa Striata).

**Results or Progress:** Based on the data, found that: 1) "Gabus fish" (Channa Striata) contained chemical substances namely: omega-3, ferrum, phospor, calcium, vitamin A, vitamin B1, and water; and 2) Chemical substance "Albumin" that was contained by "Gabus fish" (Channa Striata) can help accelerate injury healing.

**Conclusion or Discussion:** Based on the result, it was concluded that "Gabus fish" (Channa Striata) has high protein and nutrient content so that it has many health benefits. The high albumin content found in "Gabus fish" (Channa Striata) has a very important role in healing of injury after surgery.

**Keywords:** "Gabus fish" (Channa Striata), Traditional Drug, Healing of Injury

PE-070

## DONATION OF ALLOGENEIC PERIPHERAL BLOOD HEMATOPOIETIC STEM CELL: DISCOMFORT AND PHYSICAL SYMPTOMS

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**Purpose or Background:** This study was designed to provide supplementary educational materials for donors of peripheral stem cell (PBSC) transplantation. To obtain more practical and accurate information, related PBSC donors were answered to a set of questionnaires to assess donation related discomfort

**Method or Case:** From July 2016 to Aug 2017, a total of 103 PBSC donors completed the questionnaires for the assessment of discomfort and symptoms at four distinct time points of first visit to outpatient clinic, at admission, immediately after donation, and 3 weeks after donation. Donors were administered G-CSF subcutaneously at a dose of 10mcg/kg/day for 5-7 days, with 1-3 days of apheresis.

**Results or Progress:** The median age was 41years (20-66), and male and female donors were 62 (60.2%) and 41 (39.8%). Among the donors enrolled, sibling donor was the most common accounting for 66.0% (n=68), and children (22.3%, n=23), and parents (11.7%, n=12) were followed. As a result, female gender (p <.01) and middle school graduates compared to college graduate (p <.05) were more likely to show higher discomfort before donation. Insomnia and dizziness increased at admission, but all recovered after donation. Grade 1 or 2 bone pain at admission was reported in 56.2% (n=50) and 9.0% (n=8) of donors, and 44 donors (42.7%) required medication for pain control. After donation, the mean time to return to normal daily activities was 5 days, and 67 (74.4%) agreed to donate again.

**Conclusion or Discussion:** During the donor informed consent process, additional awareness of potential discomfort based on individual characteristics around donation and offering counselling services that can alleviate anticipated fear is warranted.

**Keywords:** peripheral hematopoietic stem cell, donor, discomfort, symptom

PE-071

## EFFECT OF SELF-REGULATORY FATIGUE ON COPING STYLE AND QUALITY OF LIFE OF PATIENTS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Purpose or Background:** To investigate the self-regulatory fatigue, coping style and quality of life of patients after hematopoietic stem cell transplantation, and the effect of self-regulatory fatigue on coping style and quality of life.

**Method or Case:** 114 cases of hematopoietic stem cell transplantation patients who were reexamined or hospitalized in hematology department of our hospital from January to December 2018 were investigated by using self-regulatory fatigue scale, coping style questionnaire and FACT-BMT scale (Functional Assessment of Cancer Therapy-Bone Marrow Transplantation) .

**Results or Progress:** The total score of self-regulatory fatigue in patients after hematopoietic stem cell transplantation was  $(39.80 \pm 9.31)$ . For coping style score, of which problem solving  $(5.12 \pm 1.76)$ , self-blame  $(3.71 \pm 1.28)$ , help-seeking  $(5.82 \pm 1.22)$ , fantasy  $(5.52 \pm 0.84)$ , withdrawal  $(5.64 \pm 1.11)$  and rationalization  $(6.67 \pm 1.09)$ . The total score of FACT-BMT was  $(67.52 \pm 11.84)$ . Self-regulatory fatigue was positively correlated with withdrawal in coping style ( $P < 0.05$ ), negatively correlated with problem solving and help-seeking in coping style ( $P < 0.05$ ), and negatively correlated with total score of quality of life as well as the social family status score and emotional status score of quality of life ( $P < 0.05$ ).

**Conclusion or Discussion:** The coping style and quality of life of patients after hematopoietic stem cell transplantation are closely related to the degree of self-regulatory fatigue. It provides an idea for nurses to intervene patients' self-regulatory ability correctly so as to promote patients' active coping style and improve their physical and mental health and quality of life.

**Keywords:** hematopoietic stem cell transplantation, self-regulatory fatigue, coping style, quality of life

## EFFECTIVE THERAPEUTIC PLASMA EXCHANGE FOR SEVERE CYTOKINE RELEASE SYNDROME AFTER CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY IN LEUKEMIA PATIENTS

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**Purpose:** To assess the safety and efficacy of therapeutic plasma exchange (TPE) for severe cytokine release syndrome (CRS) after chimeric antigen receptor T cell (CART) immunotherapy in patients with leukemia.

**Method:** From October 2017 to February 2019, 16 patients with refractory/relapsed leukemia who developed severe CRS after CART therapy in Beijing Boren Hospital, were treated with TPE using COBE Spectra 6.1 blood cell separator. Among them, 15 cases is refractory/relapsed B-ALL (6 cases after transplantation and 9 cases without transplantation) and 1 case is CML in blast phase. The median age was 24 (range: 3-62). Each patient received TPE for 1-3 times. For patients with PLT < 50 x 10<sup>9</sup>/L and HGB < 8g/L, platelet and erythrocyte were infused before TPE. During TPE, oral calcium gluconate 10-20ml/h was given to prevent hypocalcemia. The replacement speed was controlled to prevent hypotension. The vital signs were monitored closely during TPE. Psychological support also was provided. For adult patients, explanation of the principles, procedures and safety of TPE is necessary. Watching cartoons or listening to the stories is a good way to allay the fears of children.

**Results:** Twenty-four TPE procedures in 16 patients were performed successfully without any serious adverse reactions. After TPE, clinical symptoms, signs and laboratory parameters were improved in all patients.

**Conclusion:** Our results suggest that TPE is an effective and safe treatment for severe CRS after CART therapy. The observation of adverse reactions during TPE treatment, skilled technical operation and psychological support are the key factors for the successful implementation of TPE.

**Keywords:** therapeutic plasma exchange, severe cytokine release syndrome, chimeric antigen receptor T cell

PE-073

## EVIDENCE-BASED NURSING PRACTICE OF A PATIENT WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION COMPLICATED WITH GVHD OF HAND AND FOOT SKIN

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**Purpose or Background:** To develop a follow-up care strategy for a patient with hematopoietic stem cell transplantation complicated with graft-versus-host-disease (GVHD).

**Method or Case:** Questions were proposed based on the patients' clinical manifestations according to the PICO principle. The clinical guidelines, systematic reviews and randomized controlled trials on skin GVHD care in patients with hematopoietic stem cell transplantation were searched in Cochrane Library, PubMed, Wanfang data, and CNKI database. After evaluation of authenticity, importance, and applicability, an optimal treatment protocol was developed for the patient using the best evidence and then the patient's skin outcome was observed.

**Results or Progress:** Two days after the treatment, the patient's hand and foot rash decreased and the pain was relieved. Five days later, the swelling of the hands and feet decreased, the pain disappeared, the joint was moved flexibly, and the function of the hands and feet returned to normal. During the treatment, there was no skin lesions of the hands and feet, nor did blisters and infections occur.

**Conclusion or Discussion:** Hematopoietic stem cell transplantation patients with skin GVHD are easy to experience epidermal exfoliation, pain and infection, as well as activity limitation. Application of tacrolimus cream and hydrocolloid dressings in the early stage of skin GVHD can effectively prevent skin exfoliation and shorten recovery time, therefore to alleviate the suffering of patients and reduce the workload of nursing.

**Keywords:** hematopoietic stem cell transplantation, GVHD, Evidence-based nursing practice



## EVIDENCE-BASED NUTRITIONAL SUPPORT PRACTICE OF A HEMATOPOIETIC STEM CELL TRANSPLANTATION PATIENT WITH PANCREATITIS

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**Purpose or Background:** Hematopoietic stem cell transplantation (HSCT) has become a standard treatment option for most hematological diseases. But for the conditioning regimen, may cause severe side effects, such as mouth dryness, taste changes, vomiting, mucositis and diarrhea, resulting in insufficient oral intake and malnutrition. As malnutrition is associated with increased mortality and morbidity, poor quality of life (QOL), and prolonged length of hospital stay, nutritional support intervention is highly important. This paper introduces the evidence-based nutritional support practice for a HSCT patient with pancreatitis, so that we can better understand the issues of nutritional support in HSCT patient.

**Method:** We search the references through databases of the Cochrane library, PubMed, Medline, CINAHL, EMBASE, CNKI, CBM, the National Guideline Clearinghouse (NGC), Scottish Intercollegiate Guidelines Network (SIGN), National Institute for Health and Clinical Excellence (NICE), BMJ best practice, and Clinicalkey to collect literatures including guideline, evidence summary, best practice information sheet, recommended practice, systematic review and consensus in the last 5 years. Based on these guidelines, we conducted an evidence based nutritional support path for HSCT patient. The patient was then cared combining the actual situation with the evidence based nutritional support path, including nutritional screening and assessment, dietary counseling and nutritional education, enteral nutrition and parenteral nutrition, management of diarrhea, efficacy evaluation and follow-up of nutritional support.

**Results or Progress:** After 69 days of careful care, the patients restored oral intake, and adverse reaction was not occurred.

**Conclusion or Discussion:** Available best evidences of nutritional screening and nutritional support therapy are recommended to HSCT patients. Early nutritional assessment, appropriate nutritional support method, assessing the effect of nutritional support intervention, and ongoing follow-up are necessary for these patients, especially with the acute pancreatitis.

**Keywords:** hematopoietic stem cell transplant, pancreatitis, nutritional support practice, evidence-based nursing

PE-075

## EXPERIENCE OF PICC FIXATION IN 5 PATIENTS WITH SKIN GVHD AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Purpose or Background:** To summarize the experience of PICC fixation in 5 patients with skin graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation.

**Method or Case:** All the catheters of the 5 patients were power PICC, which was fixed in a straight manner and the scale point of catheter exposure was 0. Patients with suspected skin GVHD should be assessed daily for skin condition. Fix the patient's PICC catheter in different ways depending on the area and severity of the skin lesion in the patient. When the rash accounts  $\leq 50\%$  of the total skin area, fix with statlock combine 10×12cm dressing. Apply skin protectant before fixation to avoid Medical Adhesive-Related Skin Injury (MARSI). Daily evaluate the dressing when the dressing is loose, replace it in time. The rash accounts  $\geq 50\%$  of the total skin area or generalized erythroderma with bulla formation, the catheter was fixed to the skin with a single stitch and triple knots were tied to each perforation lateral to the securing wings (rubber clamp and retainer). The puncture point is covered with sterile gauze and replaced daily. When the patient's skin GVHD symptoms are relieved, remove the suture as soon as possible and use a statlock combine 10×12cm dressing to cover the catheter.

**Results or Progress:** Among the 5 patients, except one patient was diagnosed incorrectly, the suture fixation was not used in time, and the catheter was prolapsed 6 cm. The other patients had no complications such as Unplanned removal and infection.

**Conclusion or Discussion:** Skin GVHD occurs in patients after allogeneic hematopoietic stem cell transplantation, suture fixation can effectively fix the catheter, and regular maintenance can reduce complications.

**Keywords:** catheter fixation, skin graft-versus-host disease, suture fixation

## FACTORS ASSOCIATED WITH QUALITY OF LIFE IN PATIENTS WITH LEUKEMIA

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**Purpose or Background:** Improvement of quality of life in leukemia patients can be of a great importance. Most studies have been focusing on life expectancy rather than factors that influence quality of life in these patients. Treatment of cancer also induces fatigue in leukemia patients which also influence their quality of life. We primarily design this study to evaluate associated factors with quality of life and fatigue in leukemia patients receiving chemotherapy.

**Method or Case:** One hundred and seventy six leukemia patients referring to Shahid beheshti hospital for chemotherapy have been included in this study between 2012~2018. 36-Item Short Form Health Survey (SF-36) was used in two domains, physical and mental health.

**Results or Progress:** Mean age of patients was  $34.5 \pm 6.1$  years and 89 patients were men (50.5%). Duration of leukemia in the subjects was  $39 \pm 8.3$  months. 111 subjects (63%) had Acute Myeloblastic Leukemia, 32 (18.1%) had Acute Lymphoblastic Leukemia, 17 (9.6%) had Chronic Lymphoblastic Leukemia and 16 (9%) had Chronic Myeloblastic Leukemia. Physical component aspect of quality of life had significant association and correlation with marital status and educational level and mental component aspect of quality of life had significant association and correlation with marital status, economic status and educational level (all p values < 0.05). 166 (94.3%) of the individuals had experienced levels of fatigue. Singles showed more fatigue than married people and correlation between levels of fatigue and pain was high ( $r=0.62$ ,  $p<0.001$ ).

**Conclusion or Discussion:** Marital status, economic status and educational level of leukemia patients should be considered as important factors in their quality of life. As high rate of fatigue and pain and correlation between them, it seems to be necessary to correctly address these factors. Knowing the patient's marital status can be of the great important in managing fatigue for quality of life improvement.

**Keywords:** Leukemia, Chemotherapy, Allied Health, Quality of life

PE-077

## HEALTH-RELATED QUALITY OF LIFE (HRQOL) FOR LEUKEMIC CHILDREN USING PEDIATRIC QUALITY OF LIFE INVENTORY 4.0 GENERIC CORE SCALE (PEDSQL 4.0): LITERATURE REVIEW

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**Purpose or Background:** Survival rates of leukemia in children has improved in recent years to a 5-year survival rate. Not only is survival observed, we must analyze the Health-Related Quality of Life (HRQoL) as well. The purpose of the current study was to review articles the overall HRQoL and specific functioning subscales of children with leukemia using Pediatric Quality of Life Inventory 4.0 Generic Core Scale (PedsQL 4.0).

**Method or Case:** We identified 12 prospective reports with at least 30 participants at baseline through a search of databases of articles published from 2000 to 2018. Several articles were selected based on the articles using PedsQL 4.0 in measuring the quality of life of leukemia in children.

**Results or Progress:** The result showed that the Quality of life in children of the consolidation phase group was significantly decreased compared with of healthy controls, except in the area of emotional functioning. The maintenance phase group, the physical functioning in QoL decreased, but no differences in social functioning. QoL of children differed with treatment phase. The child's self-report and parent proxy report scores among the subscales of HRQOL were highest in social functioning and lowest in emotional functioning subscale. Different from that, leukemia children in Nepal base on the year-group showed that there are significantly problems in procedural anxiety, treatment anxiety and communication subscales than in older groups.

**Conclusion or Discussion:** So, Leukemia in children of the age specific needs should be addressed properly to improve their HRQOL overall.

**Keywords:** leukemia, Health-Related Quality of Life, review, quality of life

## IMMUNE-RELATED ADVERSE EVENTS OF CARDIOTOXICITY: A RARE NURSING CARE EXPERIENCE

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**Purpose or Background:** 26% of patients received programmed cell death 1 (PD-1) antibody or programmed death ligand 1 (PD-L1) antibody developing immune-related adverse effects (irAEs)(Wang et al., 2017). We described an immune-related cardiotoxicity in a patient with esophageal cancer who was treated with Nivolumab.

**Method or Case:** A 64 year-old male patient was diagnosed to have esophageal cancer, cT3N2M0. He received concurrent chemoradiotherapy but tumor recurrence was confirmed in February, 2018. Nivolumab 100mg fixed dose was prescribed on the 3rd and the 18th July. However, worsened dyspnea was noted on the 1st August, the chest x-ray showed dramatically enlargement of heart configuration and widened superior mediastinum (figure 1) comparing with the image 1 month ago (figure 2). Laboratory data indicated troponin-I: < 0.010ng/ml and NT-pro BNP: 473pg/ml. The echocardiography unveiled massive pericardial effusion with decreasing left ventricular ejection fraction (60.9%) (figure 3). Pericardiocentesis with 550ml pericardial effusion was performed that analysis presented Glucose: 128mg/dL, Lactic dehydrogenase: 678U/L, Lymphocyte count: 32%, cell block: no malignancy cell. Methylprednisolone 0.6mg/kg/day was prescribed since day7. 2 weeks later, his irAEs symptom improved and discharged smoothly.

**Conclusion or Discussion:** A database analysis disclosed PD-1/PD-L1 antibody related cardiotoxicity may presented as left ventricular ejection fraction dysfunction, arrhythmia, cardiac conduction disease, atrial fibrillation or ventricular tachyarrhythmia (Johnson et al, 2016). However, no prior report on pericardial effusion with normal cardiac enzyme under anti PD-1/PD-L1 treatment is published. On clinical nursing management, risk factors assessment, physical examination, cardiac enzymes tracing, 12 lead ECG, and echocardiogram for baseline measurement have to collect, furthermore, tissue biopsy for differential diagnosis also important when patient receiving PD-1/PD-L1 antibody who has a new cardiovascular events. irAEs with cardiotoxicity is a crucial issue on nursing care.

**Keywords:** Immune-related adverse events, cardiotoxicity, Nivolumab

PE-079

## IMPACT OF CIGARETTE SMOKING ON DONATED BLOOD

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**Purpose or Background:** Smoking has negative implications for health. Smoking affect the quality of blood cells through carboxyhemoglobin (COHb) levels. Cigarette smoke will go directly into the blood through the lungs without any protection from the body. This is at risk for donated blood. We conducted a systematic review of the literature to identify the effects of smoking on donated blood cells.

**Method or Case:** We searched for articles published from 2000 to 2019 to identify studies on the effects of smoking on donated blood. Of the several journals collected, 10 journals were considered potentially relevant by title and abstract and selected for full text review.

**Results or Progress:** From the paper reviewed it was found that smoking resulted in high CO concentrations. The time interval between smoking and blood donation seems to be a very important factor for increasing CO concentration. Blood cells that smoke have a greater COHb content and show an increase in hematocrit and hemoglobin after transfusion.

**Conclusion or Discussion:** We conclude that theory-driven research with a larger sample is needed to identify the subgroups of smoking intensity. This needs to be done because smoking is associated with an increased risk of death. Therefore, all efforts are made to encourage donors to stop smoking.

**Keywords:** cigarette smoking, blood donors, smoking habit

## INFECTION CONTROL USING AN INFECTION CONTROL BEST PRACTICE PROGRAM

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Infection control in HSCT in Japan is conducted at each medical institution by reference to the guidelines for early infection control after hematopoietic cell transplantation developed by the Japan Society for Hematopoietic Cell Transplantation. However, if the manual is not followed by everyone, the infection control will fail. We would like to introduce infection control using the infection control best practice "saizen", which is a program covering facets from manual development to confirmation of manual compliance, so that everyone can comply with the manual.

In the infection control best practice "saizen", clinical practitioners schematize the actual procedures, and then they consider if the procedures are evidence-based ones, and consider and decide the evidence-based procedures amongst themselves to schematize a new manual. And then, after colleagues are given training on the grounds and procedures of the new manual, they will start using the new manual. The subsequent status of compliance will be observed by others. Feedback on the observation results will be provided in the program, leading to improvement in the quality of infection control.

Case 1: Since it took time and there was variability in the operation, we undertook this for effective environmental management. To carry out cleaning from around the patient, and then from a high place to a low place, and from a clean place to an unclean place, the manual was created using photographs to show an effective method so that everyone can carry out cleaning using the same method. It reduced the time and enabled reliable environmental management by the standardized method.

Case 2: As infection frequently occurred in patients using PICC, manual development and direct observation were conducted, and the effectiveness was evaluated by surveillance. Infections decreased with improvement in the compliance rate.

**Keywords:** Infection control, Best practice "saizen", environmental management, CVC

PE-081

## INVESTIGATION OF THE HEALTHCARE NEEDS AMONG HOSPITALIZED HEMATOLOGICAL MALIGNANCIES PATIENTS

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**Purpose or Background:** As focus has shifted from disease-centered to patient-centered, patient satisfaction is being increasingly used worldwide for assessing the quality of care services provided by healthcare institutions. To understand patient satisfaction, "patient's need and perception" of care must first be understood. Therefore, we want to investigate the care need and expectations of hospitalized hematological malignancies patients.

**Method or Case:** A cross-sectional survey was performed in a convenience sample of 190 hematological malignancies patients at a teaching hospital. The data were collected (from October 2018 to January 2019) through the Comprehensive Needs Assessment Tool (CNAT), a 59-item questionnaire assessing seven dimensions of patient's healthcare needs.

**Results or Progress:** In 190 participants, the total score of CNAT was  $74.48 \pm 37.78$ , and the dimension score of health care staff, information, hospital facilities and services, social/religious/spiritual support, practical support, psychological problems, physical symptoms was  $74.48 \pm 37.78$ ,  $65.11 \pm 29.09$ ,  $55.34 \pm 27.02$ ,  $46.63 \pm 26.10$ ,  $40.83 \pm 26.01$ ,  $39.50 \pm 28.74$ ,  $27.39 \pm 26.93$ ,  $26.86 \pm 22.02$ , respectively. For the items scores, The 5 highest were 'Information about symptoms requiring a hospital visit', 'My doctor to be easy, specific, and honest in his/her explanation', 'Seeing doctor in a quick and easy way when in need', 'Collaboration and communication among health care staff', 'Being treated in a pleasant environment'.

**Conclusion or Discussion:** Patients in hematology service units have higher expectations for keeping in touch with the healthcare providers. They hope to get the disease-related knowledge and information in a convenient way. Thus, it's necessary for these stuffs to improve the humanistic care in the hospital environment, equipment and patient supporting services, in order to improve the patient satisfaction.

**Keywords:** hematological malignancy, care needs, survey, patient satisfaction



## NURSING CARE FOR ONE PATIENT WITH WISKOTT-ALDRICH SYNDROME TREATED WITH HAPLOIDENTICAL BONE MARROW TRANSPLANTATION FOLLOWING REMOVAL OF SPONTANEOUS SUBDURAL HEMATOMA

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**Purpose or Background:** To summarize the experience of nursing care for one patient with Wiskott-Aldrich Syndrome (WAS) treated with haploidentical bone marrow transplantation (haplo-BMT) following removal of spontaneous subdural hematoma.

**Method or Case:** One WAS patient was performed with haplo-BMT 24 days after removal of subdural hematoma and cranioplasty. Due to the platelet-transfusion dependent and subdural hematoma absorption, the nursing care employed for the WAS patient was comprised of a series of methods as follows, prevention and treatment of infection, prophylaxis of epilepsies, prevention for spontaneous brain bleeding, nursing WAS skin eczema, nursing operative incision in head skin, and psychological supports. The haplo-BMT was completed successfully with the comprehensive nursing cares mentioned as above.

**Results or Progress:** The WAS patient had one reconstruction of granulocyte lineage and megakaryocyte lineage at +14 days after hematopoietic stem cell infusion, and presented with a normal peripheral blood counts. The WAS patient has survived over 6 months till nowadays after haplo-BMT.

**Conclusion or Discussion:** Depending on the comprehensive nursing care, haplo-BMT for the WAS patient was successfully performed. Therefore, the nursing care experience will be beneficial to the patients with hereditary disorders, especially complicated with spontaneous subdural hematoma during haplo-BMT.

**Keywords:** Wiskott-Aldrich Syndrome (WAS), haploidentical bone marrow transplantation, subdural hematoma, nursing care for bone marrow transplantation

PE-083

## NURSING CARE OF GUT GRAFT-VERSUS-HOST DISEASE AFTER DONOR LYMPHOCYTE INFUSION FOR RELAPSED ACUTE LEUKEMIA POST ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Purpose and Background:** This case report describes the process of nursing a case of 30-years old female with mixed-phenotype acute leukemia (MPAL) suffered severe (Grade IV) Gut Graft-versus-host disease (GVHD) after donor lymphocyte infusion (DLI) for early relapsed post allogeneic hematopoietic stem cell transplantation (HSCT). Our purpose is to maximize Graft versus leukemia effect to fight MPAL and also to minimize physical and psychological discomfort caused by severe GVHD. Nursing care was provided during September 4th, 2017 to January 4th, 2018 in hematology ward. 11 days after DLI on Sep. 21st, she began with severe watery and bloody diarrhea over 2000 ml/day. Based on Gordon's 11-item functional health assessment, the patient's major problems were identified as following: diarrhea, malnutrition, existing and opportunistic infection, and grief.

**Method:** Nursing intervention is important. First of all, we established and maintained a trust relationship with the patient and her family. Second, by evaluating their physical and psychological problems, needs and stressor, the nurse provided appropriate nursing intervention to reduced physical discomfort and psychological stress and hopeless.

**Results:** The results can help the patient and their family to cope with prolonged discomfort bravely. The patient was discharged after three months on January 4th, 2018 and remained in leukemia free status successfully.

**Conclusion:** We hope that by sharing this article on the nursing experience in severe GVHD, it will serve as a valuable reference in clinical nursing care for patients who suffer from gut GVHD.

**Keywords:** Graft-versus-host disease (GVHD), Donor lymphocyte infusion (DLI), hematopoietic stem cell transplantation (HSCT), Graft versus leukemia effect

# **NUSANTARA SEHAT: THE INDONESIAN GOVERNMENT'S EFFORTS TO IMPROVE THE QUALITY OF LIFE FOR INDONESIANS**

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**Purpose or Background:** Public awareness of the importance of health is needed, to improve their quality of life. One dilemma faced was the lack of awareness from the public about their health, especially for remote communities, which made their quality of life low. Therefore, on February 3rd, 2015 the Indonesian government launched a program "nusantara sehat" as a form of the government's concern for the quality of life of its main Indonesian people for remote areas or far from vehicle access. This program was launched as one of the key priorities of the Ministry of Health. The nusantara sehat program is a primary health care strengthening program that focuses on remote communities, and team-based efforts.

**Method or Case:** descriptive analysis

**Results or Progress:** The results stated that the improvement in the quality of life of the Indonesian people were maintained. Where the statistical center in Indonesia noted an increase in the quality of life for Indonesians. In 2017-2018 the Human Development Index (HDI) increased.

**Conclusion or Discussion:** The results of descriptive analysis from several sources stated that "nusantara sehat" is one of the many effective way to make better quality of life for the community. Especially in remote areas, which is part of from the issues of the international community where all the people can join together or make the same way to increase quality of life for all people.

**Keywords:** Quality of life, Indonesia, Nusantara sehat

## OUTCOME AND QUALITY OF LIFE OF POST TRANSPLANT THALASSEMIA MAJOR PATIENTS REPORTING TO A TRANSPLANT CENTER OF RAWALPINDI, PAKISTAN

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**Background:** Quality of life (QOL) is an important and effective health care tool index. QOL assessment differs from other forms of medical assessment in such a way that it focuses on the patient's own view of physical, mental and social well-being. It documents the perceived responses on the effects of disease, health interventions and not on the disease or the condition that the patient may have. Estimates tell that 5 to 8% of the population of Pakistan are traits and every year approximately 9000 new patients are added to the population due to ineffective preventive protocols. Patients born with this disease require blood transfusions to maintain their hemoglobin levels. However due to the lack of proper medical facilities in Pakistan and noncompliance in regular blood transfusions and iron chelation, a thalassemia major child faces many transfusion related complications which lowers their overall QOL. The only curative option for a  $\beta$ -thalassemia major patient is hematopoietic stem-cell transplantation (HSCT) from human leukocyte antigen matched donor.

**Methodology:** This study assessed the QOL of thalassemia major patients who underwent HSCT in Rawalpindi at AFBMTC from 2010 to 2017 and their outcome. PedsQL questionnaire was applied to 123 out of 157  $\beta$ -thalassemia major patients who had undergone HSCT.

**Results:** Overall survival of our study population was 78.34%, thalassemia free survival was 66.2% and transplant-related mortality was 18.5% respectively. Health-related QOL scores were  $85.7 \pm 7.98$ ,  $79.59 \pm 6.24$  and  $83.2 \pm 8.58$  in physical, mental and social domains respectively. Global QOL score was  $82.83 \pm 7.6$ .

**Conclusion:** Patients who were in Pesaro risk class 3 after HSCT reported lower QOL scores when compared with other risk class. It was also noted that patients who underwent HSCT at a younger age had better QOL scores. Patients with GvHD reported lower QOL scores.

**Keywords:** thalassemia, transfusion, quality of life, hemoglobinopathies, iron chelation

## OUTCOME FOLLOWING ALTERATION OF MEDICAL ENVIRONMENT AND PROCESS AND ASSIGNMENT OF ONCOLOGY ADVANCED PRACTICE NURSE IN BLOOD AND MARROW TRANSPLANTATION CENTER

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**Purpose or Background:** This study was identified outcome alteration of medical environment that was changed to outpatient setting from focused in inpatient medical setting, improving process and assignment of oncology APNs.

**Method or Case:** We reviewed 740 patient's medical records to define number of BMT, length of hospital day for 2 years which were compared focused inpatient setting in 2008 and lots of medical process shifted to outpatient setting in 2015. Also we analyzed medical expense of patients by computer program and compared medical environment, process and role of oncology APNs.

**Results or Progress:** In part of medical environment was changed: decreased in patient beds, increased doctor's room and expansion of infusion room in outpatient clinic and assignment of Oncology APN's. Some of medical process was shifted to outpatient clinic: pre evaluation for BMT, insert of central venous catheter and bone marrow examination to define engraftment after BMT and set up the discharge criteria above ANC 1,000/ $\mu$ l. Thirteen Oncology APNs' duties were expand and engaged in medical process. The oncology APNs were assigned by hematology subspecialty. As a result, number of BMT per one BMT bed was increased to 12.4 cases in 2015 from 9.9 cases in 2008, length of hospital day was diminished 35.27days from 44.56 days.

**Conclusion or Discussion:** This study defined alteration of medical process and expansion of oncology APNs' role following expansion and moving lots of role to outpatient clinic.

**Keywords:** Oncology, Advanced Practice Nurse, Blood and Marrow Transplantation, Outpatient

PE-087

## QUALITY OF LIFE EXPERIENCE OF CAREGIVERS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION PATIENTS: A QUALITATIVE STUDY

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**Purpose or Background:** To evaluate the quality of life of the caregivers of hematopoietic stem cell transplantation (HSCT) patients and explore the influencing factors of the quality of life of the caregivers.

**Method or Case:** The descriptive phenomenological method was used to explore the quality of life of long-term caregivers of patients with HSCT in the department of hematology, first hospital of Jilin University. Semi-structured in-depth interviews with 17 caregivers were used in this qualitative study, and Nvivo software 12.0 was used to organize and code the data, and Colaizzi's seven phases of data analysis was used to form topics on the factors affecting the quality of life of caregivers.

**Results or Progress:** The quality of life of most caregivers decreased before and after transplantation, the higher medical cost led to the lower living standard, the change of patients' condition and the support of other family members affected the psychological state of caregivers, and the regular follow-up after transplantation affected the normal life of caregivers. Most caregivers are most concerned about changes in the patient's condition and want to be helped by financial, disease-related observation and care, and knowledge of prevention and treatment.

**Conclusion or Discussion:** The quality of life of caregivers of patients with HSCT has declined significantly. In the course of work, medical workers should communicate with caregivers, provide relevant support, improve the care of caregivers, ease the care burden of caregivers, and promote the physical and mental health of the caregivers and the rehabilitation of patients. In addition, it is essential to enhance people's knowledge of modern medical insurance and actively participate in commercial insurance.

**Keywords:** hematopoietic stem cell transplantation, caregiver, quality of life, descriptive phenomenological method, qualitative study

## QUALITY OF LIFE IN PATIENTS AFTER HAEMATOPOIETIC STEM CELL TRANSPLANTATION BY EORTC QUALITY OF LIFE CORE QUESTIONNAIRE QLQ-C3: A LITERATURE OF REVIEW

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**Purpose or Background:** The Haematopoietic Stem Cell Transplantation is one of the therapies that increases every year because it contributes to the improvement of patient survival. However, healing or control of the disease is often not accompanied by a full recovery of quality of life (QoL). This study aimed to reviews analyze various of the quality of life of patients after Hematopoietic Stem Cell Transplantation (HSCT).

**Method or Case:** This study used electronic database which published from 2001-2018 conducted in Germany, Brazil, Canada, Korea, Indonesia, Netherlands, and Australia. Ten articles were selected based on the articles using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire QLQ-C3 in measuring the quality of life of patients after transplantation. The collection of mean score for result EORTC QLQ-30 indicator in each article was used to see the factors that significantly influence the quality of life of patients.

**Results or Progress:** The results showed there were 15 indicators that showed the quality of life of patients based on EORTC QLQ-30. The global health, physical, emotional, cognitive, role and social function improved after HSCT was marked by the mean score of patients satisfaction of QoL over 50. Fatigue, nausea and vomiting, appetite loss, pain, constipation, diarrhea, dyspnoea, insomnia symptoms that remain at elevated levels which are indicated by the mean score of patient satisfaction below 30. Indicator of financial difficulties also showed decrease after transplantation.

**Conclusion or Discussion:** On an average from ten articles, physical function is higher and Nausea and vomiting lower on QoL. So, there are still many indicators of patients' quality of life that are declining which should be considered as a problem that persists after HSCT

**Keywords:** Quality of Life, QLQ-30, Haematopoietic Stem Cell, review

PE-089

## RELATED DONORS' EXPERIENCE FOR ALLO-HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Purpose or Background:** The aim of this qualitative study was to explore the experience of being related hematopoietic stem cell donors for allo-HSCT, to find out their motivation, emotional feelings, changes their donations bring to them, and those unmet needs.

**Method or Case:** This study used semi-structured interview to explore eighteen related donors' experience by purposive sampling. The interviews were digitally recorded, transcribed verbatim and subjected to qualitative content analysis.

**Results or Progress:** Five themes were refined: Complicated motivations to donate, No significant impacts on donors' health, Much pressure, Being anxious, Positive effects to be donors.

**Conclusion or Discussion:** Most of related donors are willing to save the patients' life, although the complex donation and transplantation process brings much pressure to donors' physical and mental health, career, study and daily life. The burden of responsibility could not be neglected. Being donors and caregivers simultaneously may be the biggest problem the donors face. Donors always suffer from anxiety because of uncertainty of patients' transplantation outcome, lack of HSCT knowledge, and long waiting and treatment process. Medical professionals should pay attention to the donors' stress problems and unmet needs, and provide sufficient education and emotional support. Our society may make efforts to help relieve the donors' family heavy burden. The donation also brings positive effects on the donors, such as outlook on life, bonding of the whole family.

**Keywords:** Allo-Hematopoietic Stem Cell Transplantation, Related donors, Donors' experience, Qualitative content analysis



## SIGNIFICANCE OF PATIENT VISIT BY NURSE BEFORE HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Purpose:** To investigate the significance of patient visit by nursing staff before hematopoietic stem cell transplantation (HSCT).

**Method:** From October 2017 to April 2019, 130 patients who underwent HSCT in our hospital were included. The first 65 cases were not visited by nurse before conditioning, and another 65 cases were visited by nurse with designed form before entering laminar air flow room to learn their clinical characteristics, psychological status and personality. The effect of patient visit by nurse pre-HSCT on nursing plan and clinical outcomes during their stay in laminar air flow room was analyzed retrospectively.

**Results:** Patient visit by nursing staff pre-HSCT was very useful for both patient and nurse. During patient visit, patients and their family members could learn more about transplant process, how to prepare items for transplant, and build up confidence for upcoming transplant. By patient visit, the nursing staff could learn more information about patient in order to make appropriate nursing plan and help patient recovery better.

**Conclusion:** Our study has indicated that patient visit by nurse before transplant is helpful to improve the quality of nursing, better relieve the pain of patients and promote recovery after HSCT.

**Keywords:** Hematopoietic Stem Cell Transplantation, Patient Visit, Nursing

PE-091

## STUDY ANALYSIS OF EDUCATE OF POST HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) SURVIVORS

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**Purpose or Background:** The hematopoietic stem cell transplantation (HSCT) is an intense chemotherapy treatment for Multiple sclerosis (MS). It aims to stop the damage caused by MS by destroying and then regenerating the immune system using your stem cells. Chemotherapy requires a long time and a process after HSCT transplantation. This study aims to reviews, analyse various of the educate of post hematopoietic stem cell transplantation (HSCT) survivors.

**Method or Case:** This study used electronic data base as a method by reviewing some previous article published in the last ten years since 2008 to 2018.

**Results or Progress:** The results showed there are various educate of post hematopoietic stem cell transplantation (HSCT) survivors like changes in their internal values and standards, optimism, social support (both from family and support groups), physical, psychological, educational quality of life (QOL) integration in the care of HCT patients. Previous research also added that the importance of education mind for survivors after HSCT because of the different complications between survivors will certainly affect the quality of life of patients.

**Conclusion or Discussion:** The education provided to survivors after HSCT is needed not only in terms of medical education but also non-medical (such as physical, social, emotional and psychological aspects). This of course will affect survivors ready to struggle to face post-HSCT complications and quality of life.

**Keywords:** study analysis, educate of post hematopoietic stem cell transplantation (HSCT), survivors

## THE APPLICATION OF FAMILY-CENTERED HEALTH EDUCATION PATHWAY IN CHILDREN'S HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Purpose or Background:** To explore the application effect of family-centered health education pathways in children with hematopoietic stem cell transplantation and their families, and to summarize nursing experience.

**Method or Case:** A total of 187 children with hematopoietic stem cell transplantation and their families who admitted to BMT unit from 2016 to 2017 were enrolled. 87 children were provided with traditional health education and 100 children were educated according to the family-centered health pathway. Take the health education time forward (pre-operative), and implement targeted and personalized education in different stages of transplantation, and strengthen the first three days of mission after admitting. The satisfaction of children and their families, the incidence of complications in children and the identity of the nurses were observed.

**Results or Progress:** The satisfaction of patient and their families increased from 96% in 2016 to 98.8% in 2017. The incidence of oral ulcers, diarrhea and other complications respectively decreased by 22.67%, 16.83%, 16.39% after implementing the family-centered health education pathway. The nurse's recognition of the path is 100%.

**Conclusion or Discussion:** The family-centered health education can effectively reduce the anxiety of patients and their families, improve the caregiver's caring ability and compliance, and nurses' satisfaction to care, and reduce the incidence of complications. Harmonize the relationship between parents inside and outside BMT unit and maximize mutual support and cooperation.

**Keywords:** family-centered, health education pathway, hematopoietic stem cell transplantation

PE-093

## THE EFFECT OF FAMILY SUPPORT AND TRUST IN MEDICAL TEAM TO IMPROVING A QUALITY OF LIFE IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

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**Purpose or Background:** Acute myeloid leukemia (AML) is the most acute leukemia that occurs in adults. As many as 80% of acute myeloid leukemia occurs in adults. Acute myeloid leukemia is a type of cancer of the blood and bone marrow. Today, the goal of treating chronic diseases including AML is to improve the ability of patients to fight their condition, so that patients can maintain an appropriate level of quality of life to continue their lives. Many studies carried out family support and trusted in medical teams as triggers to improve the quality of life of patients who later became the focus of this study. This study aims to understand how family support and trust in medical teams play a role in improving the quality of life for patients with AML.

**Method or Case:** Articles starting from 2009-2019 are collected from an electronic database. Then as many as ten selected articles were reviewed to answer the objectives of this study.

**Results or Progress:** The results of the study indicate that there is an essential relationship between family support and trust in medical teams in improving the quality of life of patients who have AML. The family will provide emotional, social and economic support so that there is an increase in motivation by patients with acute myeloid leukemia. Regarding trust in medical teams, patients will have a better perception of the quality of services that fosters confidence to improve quality of life when suffering from AML.

**Conclusion or Discussion:** It can be concluded that family support and trust in medical teams as supporting factors for improving the quality of life of AML patients.

**Keywords:** Acute myeloid leukemia, family support, quality of life, trust

## THE EFFECT OF NEUTROPENIC DIET ON PATIENTS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH EPISODES OF NEUTROPENIA: A SYSTEMATIC REVIEW

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**Background:** Neutropenic diet (ND) is prescribed to reduce risk of infection among patients with hematopoietic stem cell transplantation (HSCT). However, there's no current sufficient evidence that can prove its necessity. Besides, strict dietary guidelines could compromise patients' quality of life. Meanwhile, the Food and Drug Administration (FDA) has endorsed food safety guidelines (FSGs) for cancer patients.

**Purpose:** The aim of this study is to review literature of ND on infection rate and quality of life on neutropenic patients, and to offer medical staff with recommendations regarding dietary management on patients after HSCT.

**Methods:** A comprehensive electronic database search in EMBASE, CENTRAL, PubMed, CINAHL was performed to identify comparative studies that investigated the effect of ND compared with FSGs diet in neutropenic adults and children with cancer till May 20, 2019, with no language limitation. Outcomes of interest were infection rate and quality of life.

**Results:** Five randomized control trials (RCTs) were included after the screening. Most of them developed acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL). The definitions of ND, infections and duration of ND varied among included studies, which made pooling of results not possible. Four studies showed no significant differences between ND and FSGs diet. One study illustrated no significant differences in the number of chemotherapy cycles with total infections. Two studies explored quality of life, in which one study discovered no statistically significant differences between ND and FSGs diet.

**Conclusion:** Larger RCTs exploring infection rate and quality of life of neutropenic diet on patients with hematopoietic stem cell transplantation are needed. Before this, FDA food safety guidelines are recommended and safe to carry out, the essence of which is food-handling practices, rather than restriction of certain food.

**Keywords:** hematopoietic stem cell transplantation, neutropenia, diet, quality of life, systematic review

PE-095

## THE PRECISION NURSING STRATEGY OF CUTANEOUS GRAFT VERSUS HOST DISEASE IN ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Purpose or Background:** To summarize the precision nursing strategy of cutaneous graft versus host disease (GVHD) in allogenic hematopoietic stem cell transplantation (allo-HSCT).

**Method or Case:** Between Jan 2016 and Dec 2017, 720 patients who underwent allo-HSCT were retrospectively enrolled. 148 patients (20.6%) received HLA-matched sibling transplantation, and the others (79.4%) received haploidentical stem cell transplantation. GVHD occurred in 46.1% of all patients, and cutaneous GVHD occurred in 164 patients (22.8%). 38 patients (12.2%) suffered I° cutaneous GVHD, and 61 patients (8.5%) suffered II° cutaneous GVHD. 12 patients (1.7%) and 3 patients (0.4%) suffered III° and IV° cutaneous GVHD, respectively. Daily skin assessment, warm sponge bath with chlorhexidine acetate solution, to change bed unit and loose cotton clothes coordinating with drug treatment were used for I°-II° cutaneous GVHD. For cutaneous pruritus, Vitamin E cream were used when  $WBC > 1.0 \times 10^9/L$ , and olive oil which was dealt with microwave oven on high heat for 3 minutes and cool naturally were used when  $WBC < 1.0 \times 10^9/L$ . For III° cutaneous GVHD with blisters, disinfect with 5% iodophor solution, then pump fluid with 1ml sterile injector, disinfect again, and cover with foam dressing. For IV° cutaneous GVHD with exfoliation, Iodine coated gauze were used to fuel tissue growth when  $WBC > 1.0 \times 10^9/L$ , and nano silver ion sterile dressing were used to promote anti-infection effect when  $WBC < 1.0 \times 10^9/L$ .

**Results or Progress:** None of 164 patients with cutaneous GVHD nursing by Peking University Institute of Hematology nursing team suffered skin infection by the precision nursing strategy containing conventional combined with gradation treatments. Skin of all patients with III° cutaneous GVHD with blisters and IV° cutaneous GVHD with exfoliation were healed

**Conclusion or Discussion:** Stratified and precise nursing measures can effectively prevent infection in patients undergoing allogenic hematopoietic stem cell transplantation with skin GVHD

**Keywords:** allogenic hematopoietic stem cell transplantation, graft versus host disease, nursing

## THE RELATED FACTORS, ASSESSMENT AND MANAGEMENT OF ANXIETY IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS: AN EVIDENCE-BASED LITERATURE REVIEW.

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**Background and Purpose:** Hematopoietic stem cell transplantation (HSCT) is widely recognized as a potential cure for several hematologic neoplasms. Previous research shows that about 40% of recipients have experienced anxiety during the course of HSCT. Recipients who have anxiety may exhibit emotional fluctuations, physical symptoms and behavioral alterations. Eventually, anxiety may worsen the existing medical problems and have a negative impact on treatment-related outcomes. Thus, it is an indispensable issue to achieve a comprehensive understanding of anxiety by evidence-based literature review.

**Method:** The author integrated the literatures regarding the related factors, assessment tools and effective managements of anxiety from PubMed, Cochrane Library, CINAHL, Embase and PsycINFO databases in 1983-2019.

**Results:** The related factors that induce anxiety vary in different phases of HSCT, such as unfamiliar laminar airflow room routines and uncertain upcoming treatments in the pre-transplant phase; complications or adverse effects of conditioning regimens and various medications in the undergoing transplant phase; symptom distress, worry about relapse of disease and role changes in the post-transplant phase. Until now, many assessment tools such as State-Trait Anxiety Inventory (STAI), Hospital Anxiety and Depression Scale (HADS) and Beck Anxiety Inventory (BAI), have been available with high reliability and validity. With the evidence-based review, the effective interventions for anxiety include pharmacological therapy, cognitive-behavioral therapy, music therapy, mindfulness-based intervention, yoga and exercise.

**Conclusion:** Ultimately, this comprehensive and evidence-based literature review may establish a reference for nursing staff who care the recipients having anxiety through the HSCT process.

**Keywords:** Anxiety, Evidence-Based Literature Review, Hematopoietic stem cell transplantation

PE-097

## THE ROLE OF COMMUNICATION AND PHYSICAL ACTIVITY AS A NURSING CARE FOR STEM CELL TRANSPLANTATION PATIENTS

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**Purpose or Background:** Based on the data analyzed starting from 2008 in 104 countries, which constitute 90% of the world's population, it is indicated that around 10.800 transplants are performed every year worldwide. A stem cell transplant is a procedure that can replace damaged cells with healthy blood cells. Therefore special nursing care is needed to prevent and manage unexpected spirit and toxicity. Many studies have been carried out on nursing care on stem cell transplantations become a focus of the studies. This study aims to understand the form of nursing care as a facilitator for the recovery of stem cell transplantations patients.

**Method or Case:** This research was conducted by reviewing articles taken from reputable electronic databases. The report was as many as ten published articles in the last ten years (2009-2019).

**Results or Progress:** Based on the literature study conducted, there is a high correlation between the various roles of nurses care to the recovery of stem cell transplantation patients. The parts of nursing care divided into two, namely, communication and physical activity. From the literature study, there is excellent communication between nurses and patients is communication that contains positive stories and promotes compassionate presence. Regarding of the physical activity, from literature studies that have physical activity (i.e. practice programs, patient precautions, patient education, reduced length of stay, increased capacity, patient satisfaction scores, lower readmission rates) conducted by nurses have significant correlation to recovery after patients.

**Conclusion or Discussion:** Communication and physical activity is a role that must be performed as a form of nursing care for stem cell transplantation patients.

**Keywords:** Communication, nursing care, physical activity, stem sell transplantations



## ANAEMIA AND OTHER RBC DISORDERS PREVENTION IN INDIA - AN OVERVIEW

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**Purpose or Background:** India is a developing economy in south east Asia with population 1.32 billion (2017). The rural urban distribution is 68.84 and 31.16 respectively. It has been calculated that about half of the global maternal deaths due to RBC disorders (Anemia) occurs in South Asian countries and India alone contribute to 50 percent of global maternal death and 80 percent of maternal death in South Asian countries. As per latest World Health Organization report iron deficiency is the primary nutritional disease in the globe. Iron plays a vital role in Anaemia cause. It is the major problem for pregnant women and children. Although our government run many gross root level program and schemes to eradicate this disorder but still due to lack of medical facility, awareness toward nutrition and poverty, this is the serious concern for the Government. May program and initiatives are going on by the International and national level NGO's and government.

**Method or Case:** India is very diverse country by food stuffs, languages and dressing sense etc. Many health agencies like WHO and Ministry of Health and Family welfare, Government of India released their report of Anemia and other RBC disorder current scenario. We draw a geographical distribution of Anemia burden in India.

**Results or Progress:** The graph shows that there is a slight decrease in the no of death reported and reported patients due to anemia and other RBC disorders in last ten years.

**Conclusion or Discussion:** An awareness toward health and nutrients will play a key role to reduce the burden of anemia in India economy. There should be a public private partnership in between Government and private organizations and Government should ensure the maximum no of participant in Government program and scheme.

**Keywords:** Anaemia, India

PE-099

## BIOINFORMATICS-BASED ANALYSIS OF BIOACTIVITY OF PHYTOCHEMICALS AGAINST DENGUE INFECTIONS

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**Background:** World Health Organization estimates that major portion of world's population is at risk of infection with dengue. Cancer patients with dengue infection may have more complications such as late diagnosis, delay in next scheduled chemotherapy and may suffer the higher rate of mortality. NS3 is a dengue viral protein that functions both as a chymotrypsin like serine protease as well as an RNA helicase and RTPase too. Since NS3 is a multifunctional enzyme, inhibition of the same may result in antiviral activity and could be targeted for the development of anti-dengue drug.

**Method:** No specific antiviral treatment available for dengue fever. Leaf extracts of *Carica papaya* has been recognized as a component of traditional medication for the treatment of dengue infection in India. Thus we hypothesize that varieties of flavonoids reported in the plant may inhibit components like enzymes to prevent the infection and hence, enzyme NS3 and flavanoid interactions was studied. Bioinformatic analysis could accelerate drug candidate screening and refinement. Bioactive flavanoids including quercetin 3-(2G-rhamnosylrutinoside), kaempferol 3-(2G-rhamnosylrutinoside), quercetin 3-rutinoside, myricetin 3-rhamnoside, kaempferol 3-rutinoside, quercetin, and kaempferol were analyzed through bioinformatics-based approaches to evaluate the antiviral potency of the compounds.

**Result:** kaempferol and kaempferol 3-(2G-rhamnosylrutinoside) binds with the NS3 with high affinity. It may interfere with the RNA interactions of Arg538 NS3 structures leading to termination of reverse transcription. quercetin 3-rutinoside also interact in similar pattern.

**Conclusion:** Phytochemicals with slight structural modifications may be used as future antiviral drugs. Kaempferol could be a potent member of the same series.

**Keywords:** Dengue, Antiviral

## CASE REPORT OF GAUCHER DISEASE

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**Background:** Gaucher disease (GD) is a rare autosomal recessive genetic disorder caused by a deficiency of the lysosomal enzyme, glucocerebrosidase, which leads to an accumulation of its substrate glucosylceramide in macrophages named Gaucher cell. Infiltration of Gaucher cells in tissues can be associated with systemic pathology such as hepatosplenomegaly, pancytopenia, skin pigmentation, neurological symptoms and bone lesions.

**Purpose:** Here, we are introducing a case of GD presented by massive splenomegaly and pancytopenia in peripheral blood.

**Method or Case:** Based on the physical examination, diagnose was suspected on GD. Diagnose was confirmed by bone marrow aspiration.

**Progress:** A 23 years old female, had complained of weakness and hemorrhagic syndrome. Icterus and huge splenomegaly was observed by physical examination. Laboratory data revealed pancytopenia and severe hypochromic anemia with low regeneration. There is no changes in biochemical and coagulation tests. Gaucher cells were found in the bone marrow specimen.

**Discussion:** G.D. should be considered in the differential diagnosis of patients with unexplained splenomegaly and cytopenia with an extended period of time.

**Keywords:** Gaucher disease, glucocerebrosidase, splenomegaly, lysosomal storage disease

## COMPARATIVE OUTCOME ANALYSIS OF HOSPITAL ADMISSIONS AMONG HEMATOLOGICAL MALIGNANCIES

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**Purpose or Background:** Hospital admissions among such cases are quite frequent which includes variable causes such as diagnostic procedure, chemotherapy or post chemo- supportive care for complications. These patients usually have co-morbid conditions such as organ failure along with suppressed immune system as consequences of immunosuppressive therapy. However, there is paucity of systemic medical data to ascertain causes of hospital admissions among cases hematological malignancies. To review and analyze common causes of hospital admissions due to critical illness among cases hematological malignancies.

**Method or Case:** A detailed pubmed search yielded 33 articles with mesh phrases/terms such as ICU admissions/(5); Critically ill admissions/(6)"; Hospital admissions/(22) among acute leukemia cases was utilized. The articles which were published before year 2010 and not published in English language and were excluded out of analysis. The study has evaluated the probable causes of hospital admissions after therapy initiation in hematological malignancies. The Evaluation was predominantly based retrospective studies representing almost all geographic regions and ethnicity of people.

**Results or Progress:** The studies were predominantly retrospective and based on data collections. Outcome analysis total of 17 studies comprised of 2880 subjects of various hematological malignancies. The age ranged from paediatric to elderly age group. Few of the studies focused on parameters such as APACHE-II and SOFA scores and correlated with ICU deaths & post discharge 180 days of survival.

**Conclusion or Discussion:** The infections specially fungal and viral respiratory infections were considered as common cause of hospital admission. The factors such as need for external ventilator support, organ failures higher APACHE-II and SOFA scores were associated with higher mortality. Acute myeloid leukemia was associated with higher frequency of ICU admissions and consequent death as compared to other hematological malignancies

**Keywords:** Infections, ICU, APACHE, SOFA

## DIPEPTIDYL PEPTIDASE-IV (CD26) INHIBITION AND HEMATOLOGICAL EFFECT OF PHENOLIC RICH TRIGONELLA FOENUM EXTRACT IN TYPE 2 DIABETIC MELLITUS; IN-VITRO, IN-VIVO

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**Purpose or Background:** A novel approach in the treatment of type 2 diabetes mellitus (T2DM), based on incretin hormone which regulated by Dipeptidyl peptidase-IV (DPP-IV). As such, we hypothesized that treatment of diabetes with DPP-IV inhibitors along with hematological effects from isolated Phenolic rich Trigonella foenum (TF) extracts with different approached in-vitro; in-vivo; ex-vivo and tissue histology.

**Method or Case:** Effects of DPP-IV inhibitors from TF in high sucrose diet along with dexamethasone induced T2DM was explored in-vivo in rat. Apart from serum glucose; DPP-IV inhibition activity, HbA1c, Insulin, hepatic and renal lipid peroxidation (LPO), superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) were measured with lipid profiles to correlate hematological effects of TF with tissue histology.

**Results or Progress:** High sucrose diet with Dexamethasone administration (1 mg /kg BW 45 days) increased concentration of serum glucose, triglyceride, cholesterol and tissue LPO (renal, hepatic) with concomitant initial increase in tissue antioxidant to scavenging free radicals but after some time antioxidants such as SOD, CAT, GSH was decreased. However, after administration of Phenolic rich TF, (in-vitro) DPP-IV inhibition increase in TF (68.49%), as compared to Sitagliptin (92.16%) with significant reduction in levels of glucose, TC, TG and the hematological parameters were remained unaltered except platelet count and TLC.

**Conclusion or Discussion:** DPP-IV inhibitors isolated from TF are novel antidiabetic agents with hematological protective effects in addition to their antioxidant properties. DPP-IV inhibition lower blood glucose by increasing endogenous levels of glucagon-like peptide-1, an incretin with fewer side effects.

**Keywords:** Dipeptidyl peptidase -IV, Type 2 Diabetic mellitus, Antioxidant, Hematology, Incretin hormone

## EPIDEMIOLOGICAL PROFILING OF CANCER INCIDENCE IN INDIA DURING 2012 TO 2014: EVIDENCE FROM HOSPITAL-BASED REGISTRIES

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**Purpose or Background:** Cancer incidence in India is increasing rapidly and is the major cause of morbidity and mortality. The burden of cancer has a profound economic impact that leads to social inequity. Cancer diagnosis leads to catastrophic economic burden on the individual and it also affects the healthcare system of the country. It has profound impact on the quality of life as cancer incidence impairs the quality and quantity of life. So, in this study we aimed to understand the cancer incidence and its distribution based on hospital registries.

**Method or Case:** We screened the hospital-based cancer registries of the national cancer registry programme of 2012 to 2014. We captured the latest available data from the hospital-based cancer registries of India. The primary outcome of interest was to compute the distribution of various types of cancer incidence during 2012 – 2014 as per hospital-based registries. All the analysis was performed using STATA v12.

**Results:** A total number of 117,358 new cancer cases of which 53.6% were male and 46.4% were female reported during 2012 – 2014 from all the hospital-based registries in India. Majority of the patients were married. Cancer was diagnosed by the microscopic technique in the majority of the hospital-based registries. Among the microscopic technique, primary histology was the most common technique of cancer diagnosis. Lung cancer was the most common cancer in male while breast cancer was the most common in female among different hospital-based registries. Incidence of cancer was much higher in the age group of 35-64 years (>60%). One-third of the patients did not receive cancer-directed treatment.

**Conclusion:** Cancer incidence in India was high and one-third of the patients were deprived of cancer-directed treatment. The government should take the major step to deal with the rising incidence of cancer cases.

**Keywords:** Cancer, Epidemiology, Incidence, India, Prevalence

## ETHNOMEDICINE: EFFECTIVENESS OF RED FRUIT (PANDANUS CONOIDEUS), A TRADITIONAL HERB FROM PAPUA, INDONESIA TO CURE CANCER DISEASE

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**Purpose or Background:** Red Fruit (Pandanus Conoideus) is a traditional type of fruit originating from the area of Papua, Indonesia. Red fruit belongs to the family Pandanaceae. Traditionally, red fruit has been consumed because it is efficacious to cure various diseases. This research aims to deeply study the effectiveness of the plant as a traditional herb that may cure cancer disease.

**Method or Case:** Method used in this research was the mixed by qualitative and literature review method. Data were collected by interviews and observations of people who consumed this traditional herb. Besides that, this research was literary studies related to bioactive content in Red Fruit (Pandanus Conoideus).

**Results or Progress:** Based on the research, found that Red Fruit (Pandanus Conoideus) contained chemical compounds, namely: carotene, beta carotene, tokoferol, oleat acid, linoleat acid, omega 3, and omega 9.

**Conclusion or Discussion:** Based on the results of the research that has been done it can be concluded that the beta-carotene contained in the red fruit serves to slow the buildup of spots on the arteries so that blood flow to the heart and brain smoothly. Another study has shown that consuming beta-carotene 30-60 mg / day for two months causes the body to produce natural cells of disease killer. Increased natural cells can suppress the development of cancer cells because they can neutralize free radical of carcinogens compound cause cancer.

**Keywords:** Red Fruit (Pandanus Conoideus), Traditional Herb, Cancer Disease

## HMGB1 PLAYS A CRITICAL ROLE IN CHEMORADIOOTHERAPY-ASSOCIATED MUCOSITIS

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Oral mucositis (OM) is a common complication in cancer patients undergoing anticancer treatment. Despite the clinical and economic consequences of OM, there are no drugs available for its fundamental control. Here we show that high-mobility group box 1 (HMGB1), a "danger signal" that acts as a potent innate immune mediator, plays a critical role in the pathogenesis of OM. In addition, we investigated treatment of OM through HMGB1 blockade using NecroX-7 (tetrahydropyran-4-yl)-[2-phenyl-5-(1,1-dioxo-thiomorpholin-4-yl)methyl-1Hindole-7-yl]amine). NecroX-7 ameliorated basal layer epithelial cell death and ulcer size in OM induced by chemotherapy or radiotherapy. This protective effect of NecroX-7 was mediated by inhibition of HMGB1 release and downregulation of mitochondrial oxidative stress. Additionally, NecroX-7 inhibited the HMGB1-induced release of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-1 $\beta$ , and macrophage inflammatory protein (MIP)-1 $\beta$ , as well as the expression of p53-upregulated modulator of apoptosis (PUMA) and the excessive inflammatory microenvironment, including nuclear factor- $\kappa$ B (NF- $\kappa$ B) pathways. In conclusion, our findings suggest that HMGB1 plays a key role in the pathogenesis of OM; therefore, blockade of HMGB1 by NecroX-7 may be a novel therapeutic strategy for OM.

**Keywords:** Oral mucositis, high-mobility group box 1, NecroX-7, nuclear factor- $\kappa$ B



## IN SILICO STUDIES ON DEVELOPMENT OF NOVEL PTERIN BASE INHIBITORS AGAINST MENINGITIS DISEASE

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**Purpose or Background:** Bacterial meningitis is caused by *Neisseria meningitis* and characterized by inflammation of the lining of brain and spinal cord, has high mortality rate. Dihydropteroate synthase (DHPS), an enzyme plays a critical role in the bacterial folate metabolism which catalyzes the formation of 7,8-Dihydropteroate from p-aminobenzoic acid (pABA) and 6-hydroxymethyl-7, 8-dihydropterin-pyrophosphate (DHPP). The absence of folate pathway in higher eukaryotes makes it an attractive drug target. The pterin base inhibitors were used to target pterin site for DHPS inhibition. Further, the approach of these pterin base inhibitors towards DHPS is unknown.

**Method or Case:** Hence, the structural bioinformatics study of DHPS enzyme from *N. meningitis* was carried out using homology modeling and molecular docking techniques. The 3D model of DHPS protein of *N. meningitis* were designed using the template (PDB ID:2DQW) in Modeller9. 12v. The validation of generated model was obtained using several validation methods including Rampage, Pros and RMSD.

**Results or Progress:** The stereochemical properties of the targeted protein model were validated by Ramachandran plot using Rampage. The quality assessment of DHPS protein model with Pros revealed the Z-score value -7.86. The low RMSD observed between the target and templates reflect the presence of strong homology. It was found to be 0.80. Towards this end molecular docking was performed with Molecular Operating Environment (MOE) and pharmacophore mapping has been conducted using Accelrys Discovery studio (DS) to extract a 3D pharmacophore that reflect the important functional groups that are essential for inhibitors binding.

**Conclusion or Discussion:** The results obtained by this research work may be valuable for design of potent inhibitors for *Neisseria meningitidis* dihydropteroate synthase a promising anti-meningitis therapeutics.

**Keywords:** Meningitidis, Dihydropteroate synthase, Docking, Pharmacophore, Pterin site

## PRODUCTION OF ANTICANCER ENZYME: L-ASPARAGINASE USED IN TREATMENT OF LEUKEMIA.

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**Purpose or Background:** L- Asparaginase is used as anticancer agent in treatment of ALL and AML. This enzyme convert asparagine into aspartate and this causes death of cancer cells. Cancer cells are unable to synthesize the non-essential amino acid asparagine, whereas normal cells are able to make their own asparagine. The present study was aimed at production of L-asparaginase by using *Aspergillus niger*.

**Method or Case:** Czepek's dox medium was used for screening of fungal strains. Two fungal species were used for screening. Selected one fungal strain studied for production of L-asparaginase in coconut oil extracted cake.

**Results or Progress:** *Aspergillus niger* in the present investigation exhibited significant variation in the production of L-Asparaginase under the influence of pH and carbon sources. The enzyme activity recorded was maximum at 72 hours of incubation period with an activity of 11 IU/ml of enzyme. The optimum pH and temperature for maximum enzyme production were 9 and 40°C respectively. Molasses proved to be the best carbon source for production of L-Asparaginase.

**Conclusion or Discussion:** *Aspergillus niger* can be used for industrial scale production of L-Asparaginase. Economic sources like oil-mill waste may be used for cost effective production of this anti-cancer drug.

**Keywords:** Asparaginase, Leukemia, anticancer, *Aspergillus niger*

## PRODUCTION OF CHEMOTHERAPEUTIC PIGMENT WITH ANTICANCER AND IMMUNOSUPPRESSIVE PROPERTIES

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**Purpose or Background:** Prodigiosin is a bacterial red pigment that exhibited numerous biological activities including immunosuppressive, anticancer and antibacterial properties. It is reported to kill cancer cell lineages by either inducing caspases dependent apoptosis, DNA intercalation, altering cell signaling pathways or inhibiting the action of topoisomerase I/II. It has been showed cytotoxic effects on hepatocellular carcinoma cells, breast cancer cells and neuroblastoma cells. The present study was aimed at production of Prodigiosin using efficient microorganism.

**Method or Case:** Peptone glycerol medium (PGM) was used to screen out red colony forming bacteria from waste coconut sample. DNases, lipase, gelatinase and other biochemical tests were done to identify the isolate. Pigment production medium was used for production of Prodigiosin. Bacterial culture incubated in sterile production medium at  $28 \pm 2^\circ\text{C}$ . After incubation cell pellets were harvested and lysed by acidified methanol. Prodigiosin production was confirmed by taking absorbance at 535 nm and by HPLC.

**Results or Progress:** On the basis of biochemical tests isolated bacteria may be *Serratia* spp.. Bacteria unable to produced prodigiosin in nutrient broth but in pigment production medium did. In initial experiments, maximum concentration of prodigiosin synthesized by *Serratia* spp. was 1087 units/cell in pigment production medium.

**Conclusion or Discussion:** *Serratia* spp. and pigment production medium could be for industrial scale production of chemotherapeutic pigment Prodigiosin.

**Keywords:** Prodigiosin, Anticancer, Immunosuppressive, *Serratia*, Apoptosis, Caspase

## PROTEIN, IRON, AND VITAMIN C INTAKE WITH ANEMIA IN ADOLESCENT GIRLS IN YOGYAKARTA CITY

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**Background:** Adolescent girls are a population at risk for iron deficiency due to an increased need for iron in its infancy. The high prevalence of anemia among adolescents will continue into adulthood if not treated properly. Anemia contributes greatly to maternal mortality, premature birth, and low birth weight infants. This study is conducted to determine the correlation of protein, iron, and vitamin C intake with anemia incidence in adolescent girls in Yogyakarta City.

**Method:** This research is an analytic survey research with cross-sectional study design. The subject is adolescent girls aged 12-18 years in Yogyakarta. Measurement of hemoglobin level, MCV, MCH, and MCHC was measured using Hematoanalyzer KX-21 with Sodium Lauryl Sulphate method. Protein, iron, and vitamin C intake were measured using Semi Quantitative-Food Frequency Questionnaire (SQ-FFQ) of the last three months.

**Results:** The prevalence of anemia among adolescent girls in this study was 13.13%. 45.96% of adolescent girls have lower protein intake; 54.5% lower vitamin C intake; 86.36% lower iron intake. In this study there was no significant correlation between protein intake with anemia incidence in adolescent girls of Yogyakarta (OR 1.439; CI 95% 0.638-3.242; P=0.386), there was no significant correlation between iron intake with the incidence of anemia (OR 4.452; CI 95% 0.577-34.30; P=0.152), there was no significant correlation between vitamin C intake with the incidence of anemia in adolescent girls of Yogyakarta (OR 2.05; CI 95% 0.862-4.860; P=0.106).

**Conclusion:** The intake of adolescent girls is low, so education at schools about balance nutrition and breakfast habits is required. For adolescents, it is necessary to increase iron consumption, especially during menstruation and the collaboration between the school, the education office and the health department, such as making posters about nutrition and healthy food at schools.

**Keywords:** Protein, Iron, Vitamin C, Adolescent, Anemia, Yogyakarta

PE-110

## RARE HLA ALLELES' SIMILARITY AND DISSIMILARITY BETWEEN MAINLAND CHINESE AND TAIWANESE POPULATIONS

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**Purpose or Background:** To compare rare HLA alleles between general Taiwanese population and general Mainland Chinese population.

**Method or Case:** High resolution HLA alleles as determined by sequence-based typing.

**Results or Progress:** Please see the text of the attached Abstract.

**Conclusion or Discussion:** While Taiwanese share many rare HLA alleles in common with the Mainland Chinese, several rare HLA alleles are found to restrict to Taiwanese population.

**Keywords:** Taiwanese, Mainland Chinese, HLA, sequence-based typing, alleles

## RELATIONSHIPS BETWEEN THE RESILIENCE AND QUALITY OF LIFE OF HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) SURVIVORS

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**Purpose or Background:** In Taiwan there were 7009 hematopoietic stem cell transplantation (HSCT) survivors from 1983 to 2017. The five-year survival rate of HSCT was about 50% from 2009 to 2018. These survivors may face long-term physiological and psychosocial change. Resilience is the ability of humans to recover from changing states. The resilience of survivors of HSCT is highly correlated with their health status and quality of life. At present, there are few researches in Taiwan about this topic. Therefore, the purpose of this study is to explore the relationships between resilience and quality of life in HSCT survivors.

**Method or Case:** A cross-sectional correlation study was used 82 survivors of HSCT were recruited from a medical center in Taiwan. The HSCT survivors were asked to fill out three self-reported structured questionnaires, including the demographic medical characteristics form and the Chinese Version of the Resilience Scale and Functional Assessment of Cancer Therapy–Bone Marrow Transplantation Scale, version4 (FACT-BMT). Data were statistically analyzed with SPSS version 20.0.

**Results or Progress:** The HSCT survivors' resilience score was in moderate level. Resilience was positively correlated with FACT-BMT, FACT-G and treatment index ( $P<.01$ ). Further, the resilience also positively correlated with the domains of FACT-BMT, such as social/family health status, emotional health status, functional health status and transplant additional concerns ( $P<.01$ ). However, resilience was not significantly related to the physiological health domain of the FACT-BMT.

**Conclusion or Discussion:** Resilience is highly correlated to the quality of life. If the patient has higher resilience, the quality of life of HSCT survivors will be higher, especially for social/family health, emotional health, functional health and transplant additional concerns domains. This results provide a preliminary knowledge base on the relationship between resilience and quality of life of HSCT survivors in Taiwan.

**Keywords:** hematopoietic stem cell transplantation, survivor, quality of life, resilience

## RESULTS OF COMPARING TARGET TREATMENT DURING PRIMARY IMMUNE THROMBOCYTOPENIA

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**Purpose or Background:** Immune Thrombocytopenic Purpura /ITP/ is disorder which platelet count falls down below 100.000/mm<sup>3</sup> and it presents with signs and symptomatic tendency to hemorrhage. Worldwide it ITP incidence is approximately 3.9 per 100.000 population First line of treatment in patients with ITP is corticosteroids. In second line of treatment is treatment is chosen from choices such as splenectomy, rituximab, thrombopoietin receptor antagonist. International Working Group on ITP has developed standardized bleeding assessment score called SMOG. In last 10 years, rituximab treatment is broadly chosen as treatment of choice in patients with ITP, from meta-analysis with average follow-up of 9.5 years by Arnold O et al, a year of life without complication was 62.5%.

**Method or Case:** In this study, 21 patients/20(95%) female, (1%) male/ who had treatment of rituximab and conventional corticosteroid hormone were followed for period of 6 months afterwards which we have evaluated their results.

**Results or Progress:** Study participants 21 patients/20(95%) female, 1(5%) male/, mean age were 30.4±5.3 years old, in groups platelet count prior to treatment were 9.9±3.1 whereas 180 days post-treatment were 27.2±5.7. It is evaluated bleeding assessment score by each groups, 30 days post-treatment were higher in rituximab group, compared to corticosteroid group(p<0.05). However in late period, 180 days post-treatment mucosal bleeding were higher compared to corticosteroid group (p<0.05). When we evaluated standardized bleeding assessment score/SMOG/ and platelet count during course of treatment and post-treatment, they had medium negative /inverse/ correlation(r= -0.483, p=0.027), (r=-0.489, p=0.024). During course of treatment, bleeding symptoms increase when platelet counts decrease.

**Conclusion or Discussion:** Rituximab treatment group period of relapsed free survival were 46.2% whereas conventional corticosteroid group were 18.4%.

**Keywords:** Target treatment, hormone treatment, rituximab, platelet

## RESULTS OF MOLECULAR TARGETED THERAPY IN CHILDREN WITH CHRONIC MYELOGENOUS LEUKEMIA

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**Purpose or Background:** The purpose of the study was to summarize the clinical characteristic of pediatrics chronic myelogenous leukemia (CML) and effects of Imatinib Mesylate (IM) on three cases.

**Method or Case:** The diagnose was confirmed by the expression of BCR/ABL or Ph+ chromosome. The girls was diagnosed as CML and treated with 260-350 mg/m<sup>2</sup> per day. The clinical features of children with Ph+CML, who were treated with IM under our control were retrospectively analyzed from the time of diagnose.

**Results or Progress:** All these three cases had distended abdomen and marked splenomegaly at the time of diagnose. There were moderate to severe normocytic normochromic anemia, marked leukocytosis and thrombocytosis in CBC. Bone marrow aspiration revealed CML with blast crises. The t (9;22) could be detected and BCR/ABL was positive in these cases. All three cases achieved complete hematological and cytogenetic responses respectively 3 and 6 months later from the beginning of IM treatment. Median of follow up time is 106 months.

**Conclusion or Discussion:** CML is diagnosed at late stage of disease or stage of blast crisis. The TKI treatments are not only good tool for pediatric CML, but also cause long-term hematological and cytogenetic responses.

**Keywords:** Chronic myelogenous leukemia, tirosinkinase inhibitor, BCR-ABL gene, Imatinib Mesylate



## ROLE OF COMPLEMENT SERINE PROTEASE IN CANCER THROUGH ACTIVATION OF PLASMINOGEN-PLASMIN SYSTEM

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**Purpose or Background:** MBL-associated serine proteases (MASP-1, MASP-2, MASP-3, MASP-4, and MASP-19) are key factors in the activation of the lectin pathway of complement. The serum levels of these components were associated with colorectal, ovarian and cervical cancer. The components of the plasminogen-plasmin system participate in varieties of physiologic and pathologic processes including tumor growth, invasion and metastasis, through their effect on angiogenesis and cell migration. Since MASP-1 has wide substrate cavity, it could bind substrates other than complement pathway that may be involved in cancer growth and progression. In our study we find that MASP-1 is the activator of plasminogen-plasmin system.

**Method or Case:** rMASP-1 was expressed in BL21 (DE3) Plys cell and purified by SP-Sepharose followed by SE-FPLC Superdex 200 column. Plasminogen was digested with rMASP-1 and resulted plasmin was assayed by fibrin cleavage in comparison with control plasmin. The plasminogen and fibrinogen were also incubated with rMASP-1 in same reaction at their physiological concentration.

**Results or Progress:** Plasminogen was converted to active plasmin by rMASP-1. The plasminogen and fibrinogen incubated with rMASP-1 shows that it prefers plasminogen over fibrinogen as a substrate. rMASP-1 first digest plasminogen and convert it into plasmin, these plasmin then digests fibrinogen and already present  $\gamma$ - $\gamma$  dimer of fibrin in terminal products  $\beta''$  and  $\gamma'-\gamma'$  dimer respectively. In this reaction  $\gamma$ - $\gamma$  dimer concentration does not increase with time as seen in control reaction where fibrinogen is converted to fibrin confirmed by increase in  $\gamma$ - $\gamma$  dimer concentration with time.

**Conclusion or Discussion:** These studies conclude that MASP-1 is the activator of plasminogen-plasmin system which is involved in tumor growth, invasion and metastasis of various cancers

**Keywords:** Plasminogen, Plasmin, Serine protease, Cancer

## SIBLING ALLOGENEIC STEM CELL TRANSPLANTATION FOR CHRONIC MYELOID LEUKEMIA RESISTANT TO TYROSIN KINASE INHIBITORS AT BLOOD TRANSFUSION HEMATOLOGY HOSPITAL, VIETNAM

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**Purpose or Background:** Tyrosin kinase inhibitor (TKIs) has been the first-line therapy for chronic myeloid leukemia (CML). However, approximately 30% of patients developed resistance to first-line TKIs. Because new-generation tyrosine kinase inhibitors were hard to reach in Vietnam, allogeneic stem cell transplantation was the best treatment option for these patients.

**Method or Case:** We retrospectively analyzed 7 patients who were diagnosed as CML resistant to Imatinib or Nilotinib. They received identical or haploidentical sibling allogeneic stem cell transplantation at Blood Transfusion Hematology Hospital between Jan 2013 and Feb 2019. The conditioning regimens were BuCy or BuFlu for identical sibling and nonmyeloablative conditioning with high dose posttransplantation cyclophosphamide for haploidentical.

**Results or Progress:** Seven patients aged 24-44 years were treated with TKIs for a long period of time before transplantation (22-55 months). Secondary resistance to TKIs was determined with presence of BCR-ABL mutations on 5/7 patients: E255K, F359C, M244I and Y253H. These patients who remained chronic phase received stem cells from their siblings. The dose of CD34+ was 6,6 – 7,3 x 10<sup>6</sup>/kg. Time to neutrophil recovery was 10 – 11 days and platelet recovery was 13 – 36 days. All of them achieved complete molecular response after transplantation. There was one patient having acute GVHD and two patients develop chronic GVHD. Five of them have maintained this good response for now.

**Conclusion or Discussion:** Allogeneic stem cell transplantation has been still effective for CML resistant to tyrosine kinase inhibitors in the conditions of Vietnam.

**Keywords:** Allogeneic stem cell transplantation, chronic myeloid leukemia, resistance to TKI

## THE HEALTHCARE NEEDS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION SURVIVORS.

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**Purpose or Background:** In recent years, the survival rate of hematopoietic stem cell transplantation (HSCT) has increased which over 50% HSCT patients can live 5 years or longer in Taiwan. With the higher survival rate, survivors may face the physiological and psychosocial changes causing by HSCT. The survivors are at risk of developing long-term complication, and these complications may initiate the survivors' healthcare needs. Few studies investigated about the long-term healthcare needs of HSCT survivors in Taiwan. The purpose of this study was to explore the healthcare needs in HSCT survivors.

**Method or Case:** A cross-sectional and descriptive study design was used. 82 survivors of HSCT were recruited from a medical center in southern Taiwan. The HSCT survivors were asked to fill out two self-reported structured questionnaires, including the demographic/medical characteristics form and the Modified Chinese Short-Form Cancer Survivor's Unmet Needs. Data were statistically analyzed with SPSS version 20.0.

**Results:** Eighty-two HSCT survivors were about half male and female, with an average age of  $46.7 \pm 13.29$  years old. Survival length after transplantation was from 1.5 to 298 months, with an average of  $57.07 \pm 58.32$  months. The top score for the domains of healthcare needs for HSCT survivors were information needs domain, followed by the physical /psychological, medical care and communication needs domain. According to the intensity of healthcare needs items, the top three items were "I need to know the signs/symptoms of cancer recurrence", "I need to observe how to promote health information" and "I need assistance from medical information sources".

**Conclusion or Discussion:** It is recommended to establish a healthcare education webpage for the healthcare needs of survivors, such as the information for signs/symptoms of cancer recurrence, health promotion and importance of continue follow up. These results provide a preliminary knowledge on the healthcare needs of HSCT survivors in Taiwan.

**Keywords:** hematopoietic stem cell transplantation, survivor, healthcare need

## THE MOST IMPORTANT FINDINGS WHEN CONSIDERING BONE MARROW EXAMINATION IN PATIENTS WITH CYTOPENIA ARE ELEVATED LACTATE DEHYDROGENASE AND PANCYTOPENIA.

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**Background:** Bone marrow (BM) examinations are commonly performed to evaluate a variety of hematological abnormalities. We want to know when the BM examination was performed in real world. Especially, in patients with cytopenia, we want to find out in what circumstances BM examination would be helpful in diagnosing the hematologic diseases.

**Method:** We retrospectively reviewed the medical records of 738 patients who underwent BM examination from March 2011 to March 2019 at Soonchunhyang university Seoul hospital. We examined the 237 patients of BM examination performed to identify the cause of cytopenia except for the diagnosis of a specific disease and the evaluation of the disease status.

**Results:** We analyzed 211 patients except 26 patients with isolated thrombocytopenia who suspected immune thrombocytopenia. One hundred thirty-five patients (acute leukemia 33 patients, myeloid dysplastic syndrome 58 patients, immune thrombocytopenia 23 patients, aplastic anemia 15 patients, pure red cell aplasia 4 patients and paroxysmal nocturnal hematuria 1 patient) were diagnosed with hematologic diseases. Ten patients who had already been diagnosed with cancer were found to have bone marrow involvement, 19 patients had inflammatory marrow findings and 44 patients had non-specific marrow findings. Three patients could not be diagnosed due to suboptimal bone marrow samples. Elevated levels of Lactate dehydrogenase (LDH) beyond normal range ( $P=0.001$ ) and pancytopenia ( $P=0.001$ ) significantly increased the likelihood of being diagnosed as hematologic disease, respectively. Patients older than 65 years were more likely to be diagnosed with hematologic disease ( $P=0.074$ ). A subgroup analysis of patients with pancytopenia did not find a risk factor for the diagnosis of hematologic disease.

**Conclusion:** We have examined the case of BM examination in the real world. In case of patients with cytopenia, especially those with LDH elevation or pancytopenia, the BM examination should be considered for the diagnosis of hematologic disease.

**Keywords:** bone marrow examination, pancytopenia, Lactate dehydrogenase

## THE OUTCOME OF PATIENTS WITH RELAPSED HEMATOLOGICAL MALIGNANCY USING SECOND ALLOGENEIC TRANSPLANTATION AS A SALVAGE APPROACH POST CHEMOTHERAPY PLUS MODIFIED DONOR LYMPHOCYTE INFUSION

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**Background:** Relapse is a main problem post allogeneic hematopoietic stem cell transplantation (allo-HSCT). The outcome of Donor lymphocyte infusion (DLI) and second allo-HSCT for relapse post-HSCT have been reported. But there is no information available on a scenario in which patients relapsed post DLI.

**Method:** Here we analyzed whether a tandem approach with chemotherapy plus modified DLI (Chemo+m-DLI) and second allo-HSCT (HSCT2) for relapse after first allo-HSCT (HSCT1) could improve the outcome of the recipients.

**Results:** There were 28 patients enrolled, with a median age of 22.5 (3-48)-years-old, including 22 male and 6 female patients. With a median follow-up of 149.5 (32-1732) days, 26 patients achieved complete remission (CR) and 2 patients had persistent disease; the CR rate was 92.9%. The cumulative incidence of OS and DFS were  $25.0 \pm 8.2\%$  and  $21.4 \pm 7.8\%$  at 1 year after HSCT2 respectively. The cumulative incidence of NRM on day 100 post-HSCT2 was  $7.9 \pm 5.4\%$  and  $39.2 \pm 12.2\%$  on 1-year post-HSCT2. The risk profile prior to HSCT1 was an independent risk factor for OS post-HSCT2; And for DFS post-HSCT2, the independent risk factor was relapse within 6 months post-HSCT1.

**Conclusion:** Our findings suggest that HSCT2 could be a salvage approach for patients relapsed following Chemo+m-DLI post-HSCT1.

**Keywords:** second hematopoietic stem cell transplantation, leukemia, myelodysplastic syndromes, relapse, chemotherapy plus m-DLI

## A CASE OF CONGENITAL SIDEROBLASTIC ANEMIA DUE TO NOVEL HSPA9 MUTATION.

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**Purpose or Background:** The sideroblastic anemias (SA) are disease that characterized by ring sideroblasts in the bone marrow biopsy. The disease is composed of congenital and acquired disorders. The congenital sideroblastic anemias (CSA) are relatively uncommon and associated with mutations in mitochondrial heme-synthesis, iron-sulfur biogenesis, or protein synthesis. There are well-known gene mutations so far : ALAS2, SLC25A38, SLC19A2, GLRX5, PUS1, ABCB7, YARS2 and mitochondrial DNA deletions. However, about 40% of patients with CSA have not been found to have gene mutation. The mutations in HSPA9 are mitochondrial HSP70 homolog associated with mitochondrial Fe-S biogenesis, result in an rare autosomal recessive CSA.

**Method or Case:** Here, we report a case in which a Korean girl with HSPA9 mutation was diagnosed as CSA. A seven year-old Korean girl visited with fatigue and the initial blood test were like these ; WBC 6,130 x 10<sup>9</sup>/L, hemoglobin 5.1 g/dl, platelet 554 x 10<sup>9</sup>/L, reticulocyte 0.77%, MCV 74.1 fl, MCH 21.7 pg, MCHC 29.3 %. A bone marrow study was done due to persistent anemia and showed about 50% cellularity and ring sideroblasts. The genetic study associated with ring sideroblasts were performed and reveals HSPA9 gene mutation via direct sequencing for whole exons intron-exon boundaries of the HSPA9 gene.

**Results or Progress:** In the exon 11 region, c.1373\_1378del mutations and c.1933>T were detected. As a result of the parental test, mutation of the same pattern as the child was detected in the mother as carrier. And in the father, the c.1933>T mutation was detected in the form of homozygous conjugation. As a result of the sibling test, no mutation was observed in two elder sisters. So this girl inherited as recessive pattern.

**Conclusion or Discussion:** In our knowledge, this is the first report of congenital sideroblastic anemia associated with HSPA9 mutation in Korean.

**Keywords:** congenital sideroblastic anemia, HSPA9

## FEATURES OF THE CLINICAL MANIFESTATIONS OF VITAMIN B12-DEFICIENT ANEMIA IN YOUNG CHILDREN.

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**Purpose or Background:** Study the causes of the development of vitamin B12 deficiency in young children and the peculiarities of its clinical manifestations.

**Method or Case:** On the basis of the hematology department of the Tashkent Medical Academy, we analyzed case histories of 5 children who were hospitalized in 2017–2018. These were girls who were between 7 and 34 months old at the time of hospitalization, the average age was 19 months. The initial symptoms of the disease appeared much earlier. Myopathic syndrome with a significant lag in psychomotor development occurred in 2 children (4 months old and 6 months old, followed by a decrease in hemoglobin to 57 g / l).

**Results or Progress:** A characteristic of the clinical picture of B 12-deficient anemia in young children is the onset of the disease with symptoms of damage to the nervous system (retarded psychomotor development and myopathic syndrome), with a decrease in granulocytes a bacterial infection overlapped, anemic syndrome combined with subictericity, a moderate increase in indirect bilirubin, moderate hepatosplenitis. and high levels of LDH. All children received cyanocobalamin subcutaneously at the rate of 5 µg / kg according to clinical guidelines. Currently, they are healthy.

**Conclusion or Discussion:** Based on the analysis of our cases, it can be assumed that the development of B12-deficiency anemia in young children may be due to the absence or decrease in the content of vitamin B12 in the depot (liver) and its inadequate food intake (absence in the diet of meat products). From the literature it is known that this vitamin is absent in powdered milk and breast milk of vegetarians.

**Keywords:** vitamin B12-deficient anemia, young children, hematology department

## HAPLOIDENTICAL TRANSPLANTS FOR MALIGNANT AND NON-MALIGNANT DISORDERS IN A SINGLE PAEDIATRIC CENTER—A SOUTHEAST ASIA PROSPECTIVE

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**Background:** A major barrier to paediatric stem cell transplant in Southeast Asia has been the difficulty of finding appropriate HLA matched donor. Haploidentical stem Cells (SC) was considered after failure to find alternate source of SC.

**Objective:** To report our experience and compare outcomes in our center.

**Method:** Retrospective study from 2014 to 2018, 36 allogeneic hematopoietic stem cell transplants (HSCT) were performed.

13 T depleted haplo-identical transplants were performed for non-malignant conditions (8) and malignant conditions (5). CD3 depletion in one, TCR  $\alpha\beta$ /CD19 depletion in four, and TCR  $\alpha\beta$  with CD45RA depletion in eight. Graft source was GCSF-primed peripheral blood stem cells. Target cell doses were a minimum CD 34 cell dose of  $5 \times 10^6/\text{kg}$  and a maximum CD3/TCR  $\alpha\beta$  cell dose of  $5 \times 10^4/\text{kg}$ . GvHD prophylaxis was not prescribed if the T cell targets achieved, otherwise cyclosporine/Tacrolimus was used. Conditioning regimens were reduced intensity for majority of patients. One patient (SAA) underwent 2 TCR  $\alpha\beta$  depleted HSCT with graft rejection and eventually salvaged with a T-replete haploidentical transplant using a different parent.

**Results:** 11/13 (85%) are alive at 6 months to 5 years post-transplant. TRM 1 year was zero. 8/13 procedures achieved full donor chimerism. 4 mixed chimerism in non-malignant conditions There were 2 death: 1 patient died at 5 months from relapse of MDS/AML, the other with BMFS died at 40 months later from pneumonia associated with chest deformity.

Mean neutrophil engraftment was 15 days (9-23 days), and platelet engraftment 22 days (7-55 days). Viral reactivation was common 7/13. Skin GvHD developed in 3 (1 had grade3 liver) and graft rejection (twice in same patient) in 1/13.

During the same period, OS for the rest of allogeneic non-haploidentical HSCT was 18/23(78%) and TRM 1 year was 3/23(13%).

**Conclusion:** T-cell depleted haplo-transplantation is good option as alternate donor in multi-racial and ethnic population. The results are comparable with conventional source of SC.

**Keywords:** Haploidentical transplant, Outcome



## HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION IN PEDIATRIC PATIENTS WITH RELAPSED OSTEOSARCOMA

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**Purpose:** The overall survival (OS) of osteosarcoma with localized disease has been improved to 60 – 70%. However, the OS of relapsed osteosarcoma still remained poor around 20%. High dose chemotherapy/ autologous stem cell transplantation (HDC/ASCT) has been used in high-risk malignant solid tumor, but few studies showed the effectiveness of HDC/ASCT in pediatric osteosarcoma. We aimed to evaluate the feasibility and effectiveness of HDC/ASCT in relapsed osteosarcoma.

**Method:** We retrospectively reviewed the medical records of 6 patients who were diagnosed with osteosarcoma between 2005 and 2014 and underwent HDC/ASCT for relapsed osteosarcoma at Asan children's medical center.

**Results:** The median age of patients was 11.7 years. All patients had relapse in the lung (lung alone, n = 5; lung and bone, n = 1). The median time from diagnosis to first relapse was 23.8 months. Relapsed lesions were totally resected and salvage chemotherapy was done in all patients who achieved complete remission before HDC/ASCT. HDC/ASCT was done in two patients after the first relapse, three patients after the second relapse, and one patient after the fifth relapse. Melphalan (70mg/m<sup>2</sup>, D-6 ~ D-4), etoposide (200mg/m<sup>2</sup>, D-7 ~ D-4), carboplatin (400mg/m<sup>2</sup>, D-7 ~ D-4) were used as HDC. Grade 3-4 mucositis was noted in 5 patients. The other toxicities included hepatotoxicity (n = 3) and urinary tract infection (n = 2). CRRT was done for one patient due to acute kidney injury. No veno-occlusive disease and transplantation-related death were observed. During median follow up of 103.0 months, five patients (83.3%) remained alive after last relapse in complete remission. One patient had died of further lung relapse after ASCT as 3rd relapsed event which finally could not be removed. The estimated 5-year event-free survival and OS was 83.3% and 80.0%, respectively.

**Conclusion:** HDC/ASCT was feasible and the outcome was favorable in pediatric relapsed osteosarcoma.

**Keywords:** High dose chemotherapy, autologous stem cell transplantation, osteosarcoma, relapse, pediatric

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## HUMAN LEUKOCYTE ANTIGEN DISPARITIES REDUCE RELAPSE AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CHILDREN WITH JUVENILE MYELOMONOCYTIC LEUKEMIA.

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**Background:** Juvenile myelomonocytic leukemia (JMML) is a rare hematologic malignancy that occurs during early childhood. And most patients require allogeneic stem cell transplantation (HSCT) for long-term survival.

**Method:** We retrospectively analyzed 49 children with JMML received unmanipulated HSCT between Oct. 2008 and Oct. 2018 in our center. Median age at diagnosis was 28 months (range, 3-131 months). The source of hematopoietic stem cells was bone marrow and peripheral blood in 5 and 44 children. 40.8% (20/49) were HLA-matched whereas 59.2% (29/49) were mismatched HSCT (9 had related or unrelated 1-allele/antigen mismatched donors, 20 had two or more antigens/alleles mismatched donors or haploidentical donors). All patients received myeloablative conditioning regimen, based on cyclophosphamide and busulfan. CyclosporineA, methotrexate and Antithymocyte globulin were Graft-versus-host disease (GVHD) prophylaxis for unrelated donor, mycophenolate mofetil was plus for haploid-HSCT, additionally. and CyclosporineA alone for matched sibling donor.

**Results:** The neutrophils and platelets were recovered +13 days (10~25d) and +17.5 days (8~60d) respectively. After median follow up 27.3 months (1-114m). The 5-year cumulative incidences of chronic GVHD(cGVHD), disease free survival (DFS), non-relapse mortality (NRM) and relapse incidence (RI) were  $31.4\pm 13.2\%$ ,  $56.7\pm 7.5\%$ ,  $10.3\pm 8.6\%$  and  $33.2\pm 14.3\%$ , respectively. In multivariate analysis, diagnosis after 24 months predicted worse DFS (HR, 3.496;  $p=0.029$ ) and patient with 0 to 1 HLA disparities in the donor/recipient pair predicted higher RI (HR 3.018;  $p=0.034$ ). Compare with 0 to 1 HLA locus mismatch donor, patient with more HLA disparities (2 to 3 HLA loci mismatch or Haplo-identical) had lower RI ( $5.3\pm 10.5\%$  vs.  $51.1\pm 19.8\%$   $p=0.002$ ), but no more grades II~IV aGVHD ( $60.0\pm 22.4\%$  vs.  $31.0\pm 17.7\%$   $p=0.10$ ), cGVHD ( $30.0\pm 20.9\%$  vs.  $32.4\pm 17.7\%$   $p=0.98$ ) and NRM ( $20.0\pm 18.0\%$  vs.  $3.6\pm 7.1\%$   $p=0.06$ ).

**Conclusion:** Disease recurrence remains the major cause of treatment failure. HLA disparities graft may be beneficial to HSCT of children with JMML. Strategies to reduce relapse are warranted.

**Keywords:** Juvenile myelomonocytic leukemia, Hematopoietic stem cell transplantation, HLA disparities

## MALIGNANT SOLID NEOPLASMS OF THE CHEST ORGANS IN CHILDREN

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**Purpose or Background:** Study of the clinical and medical characteristics of the malignant solid neoplas (MSN) in children in a single-center study.

**Method or Case:** The study included 53 patients with MSN aged from 0 to 10 years who received treatment at the hematology department of the Tashkent Medical Academy.

**Results or Progress:** The ratio of boys: girls was 1: 1.5. The median age is 21.6 months (range is 0.5–73.5 months). The main group consisted of patients with NB posterior mediastinum - 45 (84.9%) cases. Another group of 8 (15.1%) patients are MSN sarcomas. The distribution in this group was presented as follows: 2/8 patients were diagnosed with pleuropulmonary blastoma, 1/8 with a fetal interstitial lung tumor, 1/8 with alveolar rhabdomyosarcoma (RMS) and 1/8 with an embryonic RMS, as well as with 1/8 of the patient has monophasic synovial sarcoma, 1/8 has a giant cell tumor of the left hemithorax and 1/8 has a case of extrarenal rhabdoid tumor. In the NB group of the mediastinum, the distribution by stages was as follows: in most cases (21 (46.7%)) 2-yastadia of the tumor process was detected, in 9 (20%) the 4th stage was established, the 3rd stage was detected less often - Eight (17.8%) children, 4 (8.9%) patients were diagnosed with 4S stage and 3 (6.6%) cases with the 1st stage of the disease. In the group of MSN sarcomas, the prevalent stages prevailed: the spreading 4th stage was found in half of the patients - 4 (50%), the 3rd stage was diagnosed in 3 (37.5%) children and the 1st stage only in 1 (12.5 %) case.

**Conclusion or Discussion:** MSN in chest organs are quite rare in childhood. Due to the low oncological vigilance in general pediatric practice, as well as the complexity of diagnosing and verifying the diagnosis, common stages of the disease prevail in the clinic. However, a complete verification of the histological diagnosis, detailed staging of the disease, the use of complex therapy (PCT, surgical treatment and RT) allows to achieve good treatment results in this group of patients.

**Keywords:** MSN, Chest organs, RMS, Hematology

## ROLE OF HYDROXYUREA IN THALASSEMIA INTERMEDIA

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**Purpose or Background:** Thalassemia intermedia is a term used to define a group of patients with  $\beta$  thalassemia in whom the clinical severity of the disease is somewhere between the mild symptoms of the  $\beta$  thalassemia trait and the severe manifestations of  $\beta$  thalassemia major. Thalassemia intermedia encompasses a wide clinical spectrum. Mildly affected patients are completely asymptomatic until adult life, experiencing only mild anemia and maintaining hemoglobin levels between 7-10g/dL. These patients require occasional blood transfusions, during acute infections or blood loss. There is currently no definitive treatment to correct the globin chain imbalance in thalassemia, but the promising approach involves the use of therapeutic agents to definitively correct the globin chain imbalance by re-activating the fetal globin genes. Hydroxyurea, a cytotoxic drug, is reported to be useful in reducing this degree of imbalance, thus decreasing the disease severity. Due to the lesser  $\alpha/\beta$  globin imbalance in  $\beta$ -thalassemia intermedia (TI), compared with thalassaemia major, better clinical responses are expected in patients with TI.

**Objective:** To determine the clinical response and frequency of side effects of hydroxyurea in thalassemia intermedia patients in local population.

**Method or Case:** Descriptive case series study was conducted in Pediatrics Department of Fatima Memorial Hospital, Lahore from August to December 2016. Total 150 patients clinically diagnosed to have thalassemia intermedia fulfilling inclusion criteria were enrolled, interviewed and examined. Baseline investigations were sent to monitor the side effects of hydroxyurea. Hydroxyurea was started at dose of 15mg/kg/day and patients were called after every fortnight for first 8 weeks and then monthly for 4 months. If no response seen on first visit, dose was increased to 20mg/kg/day and called again after 2 weeks. If still no rise in Hb observed, labelled as "no response", if Hb increase then label as according to clinical response criteria. Patients graded according to clinical response criteria after 3 months starting of hydroxyurea. For blood transfusion frequency, patients' blood transfusion record was explored for their mean pre-transfusion Hb levels and red cell consumption after and before start of hydroxyurea in 3 months. For leucopenia, complete blood count was repeated after 1 month starting hydroxyurea. For diarrhea, clinical examination and assessment was done after 1 month of starting hydroxyurea.

**Results:** Out of 150 patients, 79 (53%) were transfusion dependent and 71 (47%) were transfusion independent. Total of 123 (82%) showed response and 27 (18%) showed no response even after increasing dose from 15mg/kg/day to 20mg/kg/day. Out of 123 responders, 74 (49.3%) were good responder, 49 (32.7%)

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were partial responder. In good responders mean increment in hemoglobin ranged between 1.5g/dl to 2.5g/dl.

**Conclusion or Discussion:** Hydroxyurea is an effective and well tolerated drug for the treatment of thalassemia intermedia with very few side effects. With use of this medicine, regular blood transfusions and its hazards can be prevented in these patients.

**Keywords:** Hydroxyurea, thalassemia intermedia,, response, side effects.

## SUPERIOR SURVIVAL OF UNMANIPULATED HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION COMPARED WITH INTENSIVE CHEMOTHERAPY AS POST-REMISSION TREATMENT FOR CHILDREN WITH VERY HIGH-RISK PHILADELPHIA CHROMOSOME NEGATIVE B-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA IN FIRST COMPLETE REMISSION

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**Purpose or Background:** We explored the prognostic factors for children with very high-risk (VHR) Philadelphia-chromosome (Ph) negative B-cell acute lymphoblastic leukaemia (B-ALL) and compared the therapeutic effects of intensive chemotherapy and unmanipulated haploidentical hematopoietic stem cell transplantation (haplo-HSCT) as post-remission treatment in these patients undergoing first complete remission (CR1).

**Method or Case:** A total of 104 paediatric patients with VHR B-ALL in CR1 were retrospectively enrolled in this study, including 42 receiving unmanipulated haplo-HSCT (Group A), and 62 receiving ongoing chemotherapy (Group B). OS and DFS analysis were performed by using the Kaplan-Meier method, and were compared using two-tailed log-rank tests. CIR and NRM were calculated by accounting for competing risks. Differences in the distribution of variables were compared using the Chi-square test and Fisher exact test for dichotomous variables, and Mann-Whitney U test for continuous variables. Factors with  $P < 0.20$  in the univariate analysis were adjusted in a Cox proportional hazards model for multivariate analysis.

**Results or Progress:** Estimated 3-year overall survival (OS), disease-free survival (DFS), and cumulative incidence of relapse (CIR) of 36.2 months median follow-up were  $69.5 \pm 4.7\%$ ,  $63.5 \pm 4.8\%$  and  $32.4 \pm 4.7\%$ , respectively. Maintenance of persistent positive or conversion from negative to positive of minimal residual disease (MRD) and chemotherapy were independent risk factors associated with inferior long-term survival and higher CIR. OS, DFS, and CIR differed significantly between the groups in patients with persistent positive or negative to positive MRD.

**Conclusion or Discussion:** Haplo-HSCT may be an option for children with VHR Ph negative B-ALL in CR1, especially for patients with persistent positive or negative to positive MRD, and could achieve better survival than intensive chemotherapy as post-remission treatment

**Keywords:** Philadelphia chromosome-negative acute lymphoblastic leukaemia, children, high risk, hematopoietic stem cell transplantation, haploidentical

## T REPLETE HAPLOIDENTICAL HSCT WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE IN THREE PATIENTS WITH WISKOTT-ALDRICH SYNDROME

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**Purpose or Background:** Allogenic hematopoietic stem cell transplantation (HSCT) utilizing HLA-identical sibling donor or matched unrelated donor (MUD) HSCT and gene therapy has a long-term survival as high as 80% for Wiskott-Aldrich Syndrome (WAS) patients. In the absence of a sibling or MUD, haploidentical related donor HSCT is an option with inherent challenges of higher chances of graft-versus-host-disease (GVHD) and rejection. We present our experience of T-Replete haploidentical HSCT with post-transplant cyclophosphamide (PTCy) in three patients with WAS.

**Method or Case:** Three children (24month, 09 months and 23-month-old), with history of recurrent infections, eczematous rash and pancytopenia were diagnosed as WAS with positive sequencing for WAS gene (WAS score – 5). In the absence of HLA matched sibling, the children were taken up for T-Replete haploidentical HSCT with respective fathers as the donor (06/12 HLA matched). Fludarabine (25mg/m<sup>2</sup>/d x 5d), Busulphan (110mg/m<sup>2</sup>/d x 4d) and Cyclophosphamide 14.5mg/kg/d x 2d) conditioning regimen with PTCy (50mg/kg/d x 2d) and GVHD prophylaxis (Tacrolimus and mycophenolate mofetil) were used in all children.

**Results or Progress:** All three patients engrafted well post-transplantation between D10-D15. Patient-1 has completed D+994, and has 100% chimerism, is asymptomatic with no chronic GVHD or long-term post-transplant co-morbidities. Patient-2 had succumbed to illness due to unrelated illness at D+556 (i.e., measles). His immunoglobulin profile, cell counts were normal antemortem with 100% chimerism at D+540. Patient-3 succumbed to his illness on D+21 post-transplant secondary to necrotizing brain abscess due to free-living amoeba. Contrary to the belief, GVHD and rejection were not major challenges for Haploidentical HSCT in our settings but infectious complications were fatal.

**Conclusion or Discussion:** In the absence of sibling and MUD, haploidentical HSCT can be done with myeloablative conditioning and post-transplant in-vivo T-cell depletion using PTCy. Infections are a major challenge in resource constraint setting.

**Keywords:** Wiskott-Aldrich Syndrome, Haploidentical HSCT, Post-Transplant Cyclophosphamide, T Replete

## TANDEM HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION IN HIGH-RISK NEUROBLASTOMA: OUTCOMES AND PROGNOSTIC VARIABLES IN A SINGLE-CENTER EXPERIENCE

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**Purpose or Background:** High dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) is used for consolidation therapy in high risk neuroblastoma (HRNBL). Optimal conditioning regimens for tandem HDC/ASCT are still controversial. We retrospectively evaluate the outcome of tandem HDC/ASCT with topotecan-thiotepa-carboplatin and melphalan-etoposide-carboplatin (TTC/MEC) regimens  $\pm$  131I-metaiodobenzyl-guanidine (131I-MIBG) in HRNBL.

**Method or Case:** From March 2007 to April 2018, thirty-four HRNBL patients underwent HDC/ASCT. A regimen for first ASCT consists of topotecan (10mg/m<sup>2</sup>), thiotepa (900mg/m<sup>2</sup>) and carboplatin (1500mg/m<sup>2</sup>). We administered 210mg/m<sup>2</sup> of melphalan, 800mg/m<sup>2</sup> of etoposide and 1400mg/m<sup>2</sup> of carboplatin for second ASCT. Carboplatin dose was reduced in MIBG-combined group to 1200mg/m<sup>2</sup>.

**Results or Progress:** The median age at diagnosis was 45-month-old (range 4-month to 13-year). The 131I-MIBG treatment was added to 14 patients (41.2%). Local radiation therapy was added to 28 patients (82.4%). There were 2 treatment-related-mortalities, renal failure and pulmonary complication after second HDC/ASCT. The 5-year overall survival (OS) and event-free survival (EFS) rates of all patients were 79.3% and 69.4%, respectively. Between 131I-MIBG treated group and the other, the OS rates were 79.6%/79.1% (p-value 0.896) and the EFS rates were 69.3%/70.0% (p-value 0.891), respectively. The OS rate of MYCN-positive/-negative patients was 55.6%/93.3% (p-value 0.040), and the EFS rate of MYCN-positive/-negative patients was 55.6%/76.9% (p-value 0.036), respectively.

**Conclusion or Discussion:** Tandem HDC and ASCT with TTC/MEC regimens showed promising results, considering the current state that anti-ganglioside 2 antibody is rarely used in Asia due to its cost. Long term follow-up is needed to determine the effect of adding 131I-MIBG and further efforts are required to reduce treatment-related toxicities.

**Keywords:** autologous stem cell transplantation, high-dose chemotherapy, high risk neuroblastoma, pediatrics



## THE FIRST KOREAN PEDIATRIC CASE OF CD19-TARGETED CAR-T THERAPY FOR REFRACTORY ACUTE LYMPHOBLASTIC LEUKEMIA

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**Background:** Chimeric antigen receptor (CAR) modified T cell therapy has revolutionized the treatment of hematologic malignancies. Here we present the experience of the first Korean pediatric patient who received CAR-T therapy.

**Case:** A 6-year-old boy was diagnosed as precursor B-cell acute lymphoblastic leukemia (ALL) with central nervous system (CNS) involvement in Jan. 2014. The blast was positive for TdT, CD10, CD19, and E2A/PBX1 rearrangement. He overcame isolated CNS relapses, but relapsed in bone marrow (BM) (Aug. 2018). After the failure of blinatumomab, high dose cytarabine successfully reduced BM blast to 5%. Subsequently, he received matched unrelated PBSCT (Dec. 2018). But, day 28 BM showed persistent blast (6.8%), and recipient chimerism increased despite donor lymphocyte infusions for 3 months. Considering CAR-T therapy, he was admitted to Shanghai Children's Medical Center (SCMC) for clinical trial. Manufacture of CAR-T cells commenced in the GMP facility of SCMC on the day of leukapheresis and the incubation was completed in 7 days. A lentiviral vector was used to carry a second generation CD19-directed CAR with a 4-1BB co-stimulatory and CD3ζ signaling domains. Fludarabine/cyclophosphamide was administered for 2 days (day-5/-4). He received 9x10<sup>6</sup>/kg of CD19 CAR-T cells, and he flew back to Korea immediately after the infusion. He experienced grade 2 cytokine releasing syndrome which started about 14 hours after the infusion, but there was no CNS toxicity.

**Results:** Post-infusion day 7, BM examination showed complete remission with minimal residual disease of 0.007%. Remission and B cell aplasia have been detected for 2 months. However, dyspnea continued after infusion, and bronchiolitis obliterans was suspected at 1 month after CAR-T. He is now taking low dose steroids.

**Conclusions:** In this case, CD19 CAR-T cell eradicated refractory leukemia within 1 week. However, donor derived CAR-T cell might trigger graft versus host disease, thus further optimization is necessary.

**Keywords :** CAR-T, acute lymphoblastic leukemia, children, refractory

PE-130

## A SINGLE-CENTER EXPERIENCE OF POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD) CASES AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION(ALLO-HSCT)

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**Purpose or Background:** PTLD is a heterogeneous group of lymphoproliferative disorders, occurring in allo-HSCT recipients. In the past, PTLD was associated with significant mortality, some new treatment had markedly improved survival rate.

**Method or Case:** We retrospectively evaluated our experience of PTLD cases who underwent allo-HSCT between May, 2012 and Feb, 2018. Data of 25 PTLD cases was analyzed.

**Results or Progress:** Of 2483 patients after allo-HSCT, 25 (1%) developed PTLD. There was a trend toward increased risk of PTLD in patients received related haploidentical HSCT (1.21%, n=20), in compared with unrelated donor (0.87%, n=4) and identical-sibling donor transplantation (0.26%, n=1),  $P=0.565$ . 23 cases were early-onset PTLD, all revealed as polymorphic form by flow cytometry, in which 22 were known with Epstein-Barr virus (EBV) infection. The rest 2 cases were late-onset cases, occurred at 2 and 5 year after transplant respectively, classified by histopathological examination as monomorphic form, also had EBV infection. EBV DNAemia was  $0-5.5 \times 10^5$  copies/ml plasma, the highest concentration in tissue was  $3.5 \times 10^8$  copies/106MC. 19 patients had PTLD of B-cell origin, others had both monoclonal B-cell and plasma cell, the median percentage of monoclonal cells in peripheral blood was 0.17% (0.01%-36.57%). 24 cases were treated with reduction of immunosuppression, in combination with antiviral agent (n = 16), Rituximab (n = 13), EBV-CTL (n = 9), DLI (n = 4), or CAR-T (n = 1). 3 patients received chemotherapy. The median follow-up time was 724 (390-2123) days, 22 patients showed the effective response, with a total effective rate of 88%. 1 patient was loss of follow up, 2 (8%) patients died due to progression of PTLD.

**Conclusion or Discussion:** PTLD is a major complication of lymphoid malignancies. Reduction of immunosuppressant therapy, combined with Rituximab, cellular therapy, and chemotherapy, helped to reduce the case fatality rate of PTLD.

**Keywords:** PTLD, allo-HSCT, EBV, reduction of immunosuppressant therapy, Rituximab, cellular therapy

## BENEFITS AND PRECAUTIONS OF RUXOLITINIB IN STEROID-REFRACTORY ACUTE GVHD

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**Purpose or Background:** About half of patients become refractory to steroids and require second-line treatment. Ruxolitinib has the potential to treat GVHD in steroid-refractory (SR) patients based on retrospective clinical data. The ongoing prospective trials are currently enrolling patients to evaluate the therapeutic potential of ruxolitinib for GVHD.

**Method or Case:** We analyzed retrospectively clinical experience with ruxolitinib in patients (n=15) with grade 2~4 steroid-refractory acute GVHD patients compared with the control group (n=23) not receiving ruxolitinib. In addition, immune status was evaluated about 6 weeks ~ 8 weeks after the administration of ruxolitinib using flow-cytometry. Ruxolitinib was used as a third option for SR GVHD. And steroids were gradually decreased according to the symptoms and discontinued.

**Results or Progress:** Fifteen patients all were assessable for response. Seven patients achieved a complete response, 5 had a partial response, and 3 had no response at 8 weeks after the first ruxolitinib dose. Overall response rate was 75%. Three were treatment failures. Most adverse effects were manageable, except infectious complications. Infectious complications were occurred in about 73% patients (n = 11), resulting in two deaths. Common cause of infectious events included cytomegalovirus (n =5), herpes-zoster (n=2), Epstein-Barr virus (n=2), fungal infection (n = 2), pneumocystis jiroveci (n = 2), bacterial infections (n = 1), and pneumonia of unknown origin (n = 1). T cell counts tended to decreased in the group with ruxolitinib compared with the control group, especially CD4 cell counts.

**Conclusion or Discussion:** Ruxolitinib is effective in controlling SR GVHD and can lead to clinical benefits. However, we need to be aware of the infectious complications because ruxolitinib may lead to increased risk of opportunistic infections or reactivation of latent infections. In addition, common infectious complications are presumed to involve T cell dysfunction.

**Keywords:** Allogeneic stem cell transplantation, acute graft versus host disease, steroid refractory, ruxolitinib

## CALCINEURIN INHIBITORS REPLACEMENT BY RUXOLITINIB AS GRAFT VERSUS HOST DISEASE PROPHYLAXIS FOR PATIENTS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

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**Purpose or Background:** To determine the prophylactic value of Ruxolitinib for GVHD in Calcineurin inhibitors (CNI) intolerant patients after allogeneic stem cell transplantation (SCT).

**Method or Case:** From September 2017 to March 2019, eight patients intolerant to CNI were enrolled. The conditioning regimens were based on myeloablative BuCy regimen. Thymoglobulin 6mg/kg was applied to patients with HLA-haploidentical related donor (HRD). All of them received ruxolitinib to replace CNI as GVHD prophylaxis. Ruxolitinib was initiated at 5-10 mg BID, maintained for 2-3 months, and then tapered gradually.

**Results or Progress:** The patients were aged 16-50 years old, including six acute leukemia (AL), one MPN and one NK/T lymphoma. The donors were from matched sibling donors (MSD, n=3) and HRD (n=5). They firstly received CNI plus short-time methotrexate as GVHD prophylaxis, but all showed intolerance within 45 days after SCT. The reasons for CNI withdrawal were transplantation-associated thrombotic microangiopathy (TMA, n=4), CNI-induced pain syndrome (n=2), CNI-related hepatic toxicity (n=2).

The median interval from SCT to ruxolitinib was 39 (range: 30- 48) days. After replacement of CNI by ruxolitinib, only one patient (12.5%) developed grade II skin aGVHD, and no one developed severe aGVHD. Among seven patients surviving beyond day+100, three (42.8%) developed cGVHD, upon ruxolitinib tapering. The one-year moderate /severe cGVHD rate was 28.6%.

III-IV Cytopenia was observed during ruxolitinib in one patient, which was complicated with pulmonary infection/B19 viremia. Cytomegalovirus-reactivation occurred in two patients. The 100-day accumulative TRM were 12.5%. After a median follow-up of 11 (range: 2-14) months, two of eight patients (25%) relapsed at +8 month and +10 month. Both were transplanted from MSD at CR2/CR3. Five (62.5%) patients were alive with negative MRD and good general condition.

**Conclusion or Discussion:** This experimental study shows the prophylactic application of ruxolitinib for CNI-intolerant patients after allo-SCT is especially effective to prevent aGVHD, with mild side effect.

**Keywords:** Ruxolitinib, Graft vs. Host Disease (GVHD), Allogeneic Stem Cell Transplantation (SCT), Calcineurin Inhibitors

## CLINICAL EFFECTS AND MICROBIOME DIVERSITY CHANGES OF FECAL MICROBIOTA TRANSPLANTATION IN A PATIENT WITH SEVERE ACUTE GRAFT-VERSUS-HOST DISEASE OF THE GUT

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**Purpose or Background:** This study was aimed to explore the intestinal tract microbiome in immunodeficiency patients and find a safely and effectively novel treatment of gut aGVHD.

**Method or Case:** A 5-year-old boy diagnosed as Fanconi anemia received hematopoietic stem cell transplantation (HSCT) at SCMC in May 2017. He began to suffer severe gut acute Graft-versus-Host Disease (aGVHD) from 11 days after HSCT. Due to poor effect of regular treatment on GVHD, we performed fecal microbiota transplantation on him at the 69th and 70th day after HSCT. The fecal samples were collected on specific time in order to have a better understanding of how microbiome changes before and after severe gut aGVHD. Bacterial 16S rRNA gene sequences were characterized, and alpha and beta bacterial diversity was estimated.

**Results or Progress:** The patient's diarrhea symptom was unstable within the first month after FMT and grew better thereafter. Before his discharge (in the ninth week after FMT), he already had a remission with normalized stools. Under the 21 months' following-up, the patient is still undergoing a medication of methylprednisolone as the therapy for chronic GVHD of skin, no lower gastrointestinal abnormality has been observed. The lowest bacterial alpha diversity was analyzed when gut GVHD occurred and highest on the 14th day after FMT. Although the alpha diversity on +3day, +28day and +120day after FMT shared similar to those when GVHD occurred, their beta diversity was different. Microbial community barplot helped us find a composition changes among first till second month after FMT and a trend to return to original abundance with different community.

**Conclusion or Discussion:** Individual fecal microbiota transplantation was proved to be safe and feasible. The improvement of fecal microbiome after fecal microbiota transplantation proves the repair effect of intestinal flora on the intestinal tract.

**Keywords:** Hematopoietic stem cell transplantation, gut aGVHD, fecal microbiota transplantation, Intestinal microbiome, Bone marrow failure

## DRUG USE EVALUATION OF OPIOID ANALGESICS IN PAIN MANAGEMENT AMONG PATIENTS WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Purpose or Background:** Hematopoietic stem cell transplantation (HSCT) patients usually experience severe mucositis and musculoskeletal pain due to conditioning regimens containing high dose chemotherapy or radiation and post-HSCT infection or graft-versus-host disease. Pain management is important for the quality of life of the patient. The purpose of this study was to evaluate the appropriate use of opioid analgesics in HSCT patients and to propose effective pain management strategies.

**Method or Case:** A retrospective analysis was conducted using electronic medical records of adult HSCT patients who were treated with opioid analgesics for moderate to severe pain in Seoul National University Bundang Hospital. Appropriate use of opioid analgesics was evaluated following published guidelines for cancer pain management.

**Results or Progress:** A total number of 119 cases were evaluated, and 369 episodes were recorded with moderate to severe pain. The 57.8% of 369 episodes were mucositis-related pain, 25.8% were musculoskeletal pain and 10.2% were headache. The most frequently used opioid analgesics was intravenous tramadol (84.9%) followed by fentanyl patch (73.9%) and intravenous morphine sulfate (68.9%). Intravenous and topical administrations were mainly used for mucosal pain. 95.0% of the patients were prescribed with appropriate short-acting opioid analgesic for initial pain control, 80.5% received appropriate dose of short-acting opioid analgesic, 95.5% were adjusted with appropriate dose of analgesic after the assessment of first response, 85.6% were converted to appropriate long acting opioid analgesic.

**Conclusion or Discussion:** The use of short-acting opioid analgesic for initial pain management and dose adjustment after assessment were appropriate. However, when converting to long-acting opioid analgesic, it is difficult to follow the guideline conversion dosage as it is, considering the clinical situation of HSCT patients who have difficulty taking oral preparation. For appropriate dosage conversion and effective pain management, pain management guidelines for HSCT patients is required.

**Keywords:** drug use evaluation, opioid analgesics, pain management

## EFFICACY OF INTRAPULMONARY ADMINISTRATION OF THROMBIN IN HEMATOLOGICAL MALIGNANCY PATIENTS WITH ALVEOLAR HEMORRHAGE

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**Purpose or Background:** Alveolar hemorrhage (AH) is characterized by the acute onset of alveolar bleeding and hypoxemia. Thrombin has been widely used to achieve coagulation and hemostasis. However, the efficacy of thrombin in patients with AH is unclear. Thus, this study aimed to evaluate the efficacy of thrombin administration in patients with AH.

**Method or Case:** This retrospective study included 15 hematological malignancy patients with AH who received intrapulmonary thrombin between March 2013 and July 2018.

**Results or Progress:** All patients received thrombin (1,000 IU/ml) via a fiberoptic bronchoscope within 3 days after starting mechanical ventilation, and it immediately controlled the AH in 13 of 15 patients. The PF ratio improved in 10 of 15 patients, and the mean PF ratio was significantly higher after thrombin administration than before administration ( $p = .03$ ).

**Conclusion or Discussion:** In conclusion, thrombin administration effectively controls bleeding and may be a good therapeutic option in hematological malignancy patients with AH.

**Keywords:** alveolar hemorrhage, hematologic malignancy, intrapulmonary thrombin

## EVALUATION OF THE IMPACT OF ABO COMPATIBILITY IN HEMATOPOEITIC STEM CELL TRANSPLANTATION: A SINGLE CENTER EXPERIENCE FROM PAKISTAN

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**Background:** Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative option for a variety of hematological diseases. ABO incompatibility may have an effect on the clinical outcome after transplantation. The aim of the study is to evaluate the impact of ABO compatibility in hematopoietic stem cell transplantation.

**Method:** A prospective observational study was conducted in our Institute for a period of 2 years from June 2016-2018. Patients were categorized according to ABO compatible and mismatched groups. Direct coomb's test (DCT), serum Lactate dehydrogenase (LDH) and liver function tests (LFTs) were performed.

**Results:** A total of 85 patients were enrolled in the study. Out of these, 54(63.5%) were male and 31(36.5%) female. Mean age was (6.99±4.6) in both groups. Indications for transplant included beta thalassemia major 53(60.2%), aplastic anemia 25(28.4) and pure red cell aplasia 2(2.35%). Neutrophil and platelet engraftment was achieved in ABO matched group on Day +12 and Day +14 respectively while in other group it was achieved on Day +13 and Day +17. In the post transplantation period, red blood cells and platelets were transfused in matched group (n=401) and (n=1,837) respectively in comparison to (n=102) and (n=480) in mismatched group respectively. Primary and secondary graft failure in matched group was 8.77% and 12.28% patients while in mismatched group graft failure was observed in 4(14.28%) and 4(14.28%) patients respectively. One patient had positive DCT in ABO matched while two patients in the ABO mismatched group observed via raised LDH levels and deranged LFTs. Episodes of acute and chronic Graft versus Host Disease (GvHD) in both groups were insignificant. Overall survival in ABO mismatched was higher than the ABO matched group (85.7% and 78.4%).

**Conclusion:** These results indicate that ABO incompatibility does not seem to influence outcome of the patients undergoing HSCT.

**Keywords:** hematopoietic stem cell transplantation, ABO compatibility, Graft versus Host Disease, Direct Coomb's test, Lactate dehydrogenase, engraftment



## EXPLORE THE RELATIONSHIP BETWEEN INTESTINAL FLORA CHANGES AND GUT AGVHD AFTER HSCT

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**Purpose or Background:** To investigate the relationship between intestinal flora changes and gut aGVHD after HSCT

**Method or Case:** This was a cross-sectional case study of children from SCMC from July 2016 to January 2017. 16s RNA sequencing of feces were completed before or after HSCT for patients. And the healthy control cases were also measured. The clinical data of diarrhea were retrospectively analyzed, so as the risk factors of survival. LEfSe and statistical analysis were carried out with the bio-information of feces.

**Results or Progress:** A total of 56 samples of 42 patients and 6 normal children's samples met study criteria and were selected for analysis. Patients' characteristics, transplant conditions, clinical manifestations and severity of diarrhea were not statistically associated with diarrhea type. The alpha diversity of the GVHD group was the lowest, which was statistically significant compared to the non-diarrhea group (P value=0.032). A richer post-transplantation relative-abundance of Moraxellaceae was conducive to survival, while that of Enterococcaceae and Alphaproteobacteria were not. Similarly, a rich relative-abundance of Proteobacteria, Gammaproteobacteria and Odoribacteraceae in intestinal flora before HSCT contributed to patients' death thereafter. In respect of diarrhea, the GVHD group was discovered a richer relative-abundance of Pasteurellales and Pasteurellaceae, which showed a strong coeffect with diarrhea severity. Peptostreptococcaceae, Bifidobacteriales and Bifidobacteriaceae were richer in relative-abundance from the intestinal infection group and correlated to pre-transplant-characteristics.

**Conclusion or Discussion:** The gut microbiota diversity was lowest when gut aGVHD occurred, which was consistent with the clinically higher mortality rate and greater treatment difficulty. Pasteurellaceae played an important role in gut aGVHD and the severity of diarrhea. Specific bacteria were biomarkers for survival: Moraxellaceae, Enterococcaceae and Alphaproteobacteria from intestinal flora after HSCT and Proteobacteria, Gammaproteobacteria and Odoribacteraceae before HSCT.

**Keywords:** Hematopoietic stem cell transplantation, gut aGVHD, Post-transplant infection, Intestinal microbiome

## GRAFT-DERIVED RECOVERY OF MUCOSAL-ASSOCIATED INVARIANT T CELLS AFTER MYELOABLATIVE ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Purpose or Background:** Mucosal-associated invariant T (MAIT) cells are recently discovered “innate-like” T cells, which represent up to 10% of the peripheral T cell repertoire and are particularly abundant in the liver and intestine. Roles of MAIT cell subsets in immune reconstitution and acute graft versus host disease (aGVHD) after hematopoietic stem cell transplantation (HSCT) are poorly defined.

**Method or Case:** Mucosal-associated invariant T (MAIT) cells are recently discovered “innate-like” T cells, which represent up to 10% of the peripheral T cell repertoire and are particularly abundant in the liver and intestine. Roles of MAIT cell subsets in immune reconstitution and acute graft versus host disease (aGVHD) after hematopoietic stem cell transplantation (HSCT) are poorly defined.

**Results or Progress:** A rapid increase to a plateau at day 30 after HSCT was due in part to proliferation of MAIT cells transferred in the HCT graft. The occurrence of acute GVHD and use of steroids significantly impaired MAIT cell reconstitution ( $p=0.0042$ ). Age, sex, underlying disease, conditioning regimen, donor type, infections, and pre-HSCT MAIT cell values were not associated with recovery of MAIT cells. However, recipients with high levels of pre-HSCT ( $p=0.006$ ) and graft ( $p=0.017$ ) MAIT cells showed significantly lower risk of aGVHD.

**Conclusion or Discussion:** The quantity of MAIT cells in graft carried a significant impact on the early post-HSCT course. Pre-HSCT and graft MAIT values were possible regulatory factors of pathogenesis of aGVHD.

**Keywords:** Mucosal-associated invariant T cells, acute graft versus host disease, hematopoietic stem cell transplantation

## HAPPINESS AND ROLE OF VITAMIN D IN CHILDREN ON CHEMOTHERAPY

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**Purpose or Background:** Bone marrow transplantation is established successful treatment for several pediatric hematologic diseases and because of immunosuppressive, activity avoidance, malabsorption and organ function compromises which may be a factor in causing unhappy situation with lack of smile and happiness for the child. Resulting various psychosocial problems, because of mood elevating serotonin deficiency a neuroactive compound which regulates cell differentiation, proliferation, and peroxidation in brain. There are evidences that vitamin D elevates mood by activating cortisol and serotonin cycle resulting positive energy and happiness which prompted us to present study of prevalence of happiness and its relation to vitamin D.

**Method or Case:** We studied 6 children aged 5--9 years who undergone bone marrow transplant for haemopoietic disorders and presented with depressive unhappy mood alteration, were evaluated with modified Oxford happiness questionnaires. We conducted vitamin D levels and start on oral vitamin D supplement with 4000 IU per day were followed accordingly flow chart

**Results or Progress:** All six children were vitamin D deficient, were in unhappiness score, followed up it was observed that compliance for vitamin D intake was good, clinical improvement with improving happiness score. Repeat serum vitamin D level showed improved results

**Conclusion or Discussion:** The beneficial effects of vitamin D may extend beyond the effects on immune system but also on serotonin activation pathway resulting in improving mood related disorder. The present study prevalence of happiness and its relation to vitamin D in children with post bone marrow transplant has shown positive results. Large studies may be done for further evaluation

**Keywords:** Vitamin D, serotonin, Happiness, Post-chemotherapy

## LONG-TERM FOLLOW-UP OF PATIENTS WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION: THE ROLES OF CASE MANAGERS

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**Purpose or Background:** Hematopoietic stem cell transplantation (HSCT) is a curative treatment modality for hematologic malignancies but with various complications, including financial burden, graft-versus-host-disease (GVHD), infection, and psychological stress. Our institute sets up transplant case managers (CM) to improve long-term care quality.

**Method or Case:** CMs review charts and visit patients, focusing on GVHD and hepatitis B. The time points include before HSCT, after HSCT but before discharge, one week after discharge, and once every 3 months within the first year, once every 6 months between 1-2 year. Autologous cases will be followed for 6 months.

**Results or Progress:** Between January 2015 and December 2018, a total of 589 patients were enrolled. The most common disease is leukemia (48.2%), followed by lymphoma (33.8%). Autologous HSCT composed of 28.5% of the cohort. Among the rest, 71.5% of patients receiving allogeneic HSCT, the percentage of matched unrelated donor (MUD) transplant decreased with the time, in contrast to the gradually increasing haploidentical HSCT. The percentage of patients older than 50-year-old also increases gradually.

The total times of visits were 7,977; 91% from recipients and 44.3% incoming calls. Most incoming calls were in the 6 months after HSCT, followed by 12-18 months after HSCT, majorly for chronic GVHD. The major contents of recipients' incoming calls: for symptom (43%), for medications (7%), and for diet (6%). The most common involved organ include skin, gastrointestinal tract, and oral cavity.

**Conclusion or Discussion:** During the past four years, we found the increasing recipients' age and haploidentical donor source. We can enhance the care guidance for the chronic GVHD. In a multidisciplinary HSCT team, the CM can provide cares for different periods after HSCT, and might improve the patients' quality of life.

**Keywords:** LONG-TERM FOLLOW-UP, CASE MANAGER, HEMATOPOIETIC STEM CELL TRANSPLANTATION

## OBESITY IS CORRELATED WITH POOR OUTCOME AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH ACUTE LEUKEMIA

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**Purpose or Background:** The relationship between nutritional condition and outcomes after allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains controversial due to previous studies. While the majority of studies were conducted in western countries, studies concerning the correlation of body mass index (BMI) on transplantation outcome in Asian recipients are limited.

**Method or Case:** We retrospectively analyzed 634 acute leukemia patients received allo-HSCT at our center from 2008 to 2017. We utilized the BMI criterion proposed by Chinese institution: <18.5 kg/m<sup>2</sup> (underweight); 18.5–23.9 kg/m<sup>2</sup> (normal-weight); 24.0–27.9 kg/m<sup>2</sup> (overweight); ≥28 kg/m<sup>2</sup> (obese). In addition to the quartile classification, we combined the underweight and normal-weight groups as lower BMI group, as well as the overweight and obese groups as higher BMI group.

**Results or Progress:** The distribution of patients in different categories of BMI showed that 57.1% of patients had normal BMIs, whereas 15.9% were underweight, 21.1% were overweight and 5.8% were obese. With long-term follow-up, when compared with normal-weight patients, the probability of overall survival (OS) was significantly lower in overweight (p=0.010) and obese patients (p=0.013). The results demonstrated that higher BMI was associated with poorer OS (RR (relative risk): 1.66; 95% CI: 1.23–2.23, p<0.001) and shorter leukemia free survival (LFS) (RR: 1.62; 95% CI: 1.23–2.14, p<0.001). Additionally, patient exhibiting a higher BMI was more likely to face the problem of relapse (30.1% vs 21.6%, p=0.001). Furthermore, obese patients' non-relapse mortality (NRM) was statistically higher than other three subgroups (24.3% vs 10.2%, p=0.047). Besides, individual with a higher abdominal girth (AG) tend to survive shorter (RR: 1.60; 95% CI: 1.20–2.14, p<0.001) with higher relapse rate (p=0.095).

**Conclusion or Discussion:** Our results indicated that obesity at pre-HSCT stage whether characterized by higher BMI or AG is correlated with poorer survival.

**Keywords:** Acute leukemia, allogeneic hematopoietic stem cell transplantation, body mass index, abdominal girth

## POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME IN HSCT FOR HEMOGLOBINOPATHIES

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**Introduction:** Hematopoietic cell transplantation (HSCT) is the only curative treatment for thalassemia major (TM) and sickle cell disease (SCD). Cyclosporine and Tacrolimus are used for prevention of GvHD. Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological entity that is characterized by headache, visual disturbances, mental status changes, seizures, and coma; accompanied by radiologic findings showing a posterior-predominant pattern of bilateral gray and white matter edema. The incidence of PRES in children post organ transplant or HSCT ranges from 1% to 10% & 1% to 8% for adults.

**Method:** This is a retrospective analysis of patients with TM and SCD who underwent transplant at our institute between February 2010 to April 2019. A total of 22 patients that developed PRES 15 underwent MRD HSCT and 7 underwent Haplo HSCT. Conditioning was either Bu/Cy/ATG for MRD HSCT and Thymo/Flu /Bu for Haplo HSCT. GvHD prophylaxis was CSA+MTX or TAC/MMF/PTCy.

**Results:** Out of 253 HSCT, 22 patients (8.7%) developed PRES; 16 patients out of total 215 (7.4%) were with TM and 6 patients out of total 38 (15.8%) were of SCD with median age of 10 years (4-26). At a median follow up of 40 months (78-3282 days); the OS and DFS for TM patients with PRES was 81.25% and 75% respectively and 88% and 80.5% for patients without PRES. For SCD patients with PRES, the OS and DFS at a median follow up of 12.5 months (50-713 days) was 83.3% and 66.7% respectively and 92% and 82% for patients without PRES. Mortality: 18.75% in TM and 16.7% in SCD with PRES.

**Conclusion:** PRES should be considered in patients presenting with hypertension, seizure or other neurological symptoms post HSCT. SCD patient have higher incidence of PRES possibly due to associated sickle cerebral vasculopathy. The overall outcome is good without long term neurological sequelae.

**Keywords:** PRES, haemoglobinopathies, sickle cell disease

## PREEMPTIVE INTERFERON- $\alpha$ TREATMENT COULD PROTECT RELAPSE AND IMPROVE LONG-TERM SURVIVAL OF ACUTE LEUKEMIA PATIENTS AFTER ALLOGENEIC HSCT

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**Purpose or Background:** Previous studies reported that preemptive interferon- $\alpha$  (IFN- $\alpha$ ) treatment can help clear minimal residual disease (MRD) after allogeneic hematopoietic stem cell transplantation (allo-HSCT), but the long-term efficacy was unknown. Thus, we aimed to identify the long-term clinical outcomes of preemptive IFN- $\alpha$  treatment in acute leukemia patients who had MRD after allo-HSCT (n=118)

**Method or Case:** MRD was monitored by multiparameter flow cytometry (MFC) and polymerase chain reaction (PCR). A patient was considered to be MRD-positive when a single bone marrow sample tested positive by PCR or MFC. Recombinant human IFN- $\alpha$ -2b injections were administered subcutaneously for 6 cycles (twice or thrice weekly in every 4-week cycle). The study was registered at <http://clinicaltrials.gov> as #NCT02185261 and #NCT02027064. This work was supported by the Capital's Funds for Health Improvement and Research (grant number 2018-4-4089)

**Results or Progress:** The 4-year cumulative incidence of relapse and non-relapse mortality after IFN- $\alpha$  treatment was 16.1% (95% CI, 9.4–22.8%) and 5.6% (95% CI, 1.1–10.1%), respectively. The 4-year probabilities of disease-free survival and overall survival after IFN- $\alpha$  treatment were 78.3% (95% CI, 70.6–86.0%) and 84.0% (95% CI, 77.1–90.9%), respectively. In MRD-positive patients, the clinical outcomes of patients receiving preemptive IFN- $\alpha$  treatment were better compared with those without any interventions.

**Conclusion or Discussion:** This extension study is the first to confirm the long-term efficacy of preemptive IFN- $\alpha$  treatment after allo-HSCT. In addition, this is the largest study confirmed that IFN- $\alpha$  can indeed induce clinically relevant antileukemic responses in acute leukemia patients. Thus, preemptive IFN- $\alpha$  treatment was giving the right treatment to the right patients at the right time, which can both unlock the therapeutic potential of IFN- $\alpha$  in acute leukemia and spare the patients in remission from further therapy. Importantly, IFN- $\alpha$  treatment can also be performed conveniently on an outpatient basis without severe toxicity.

**Keywords:** acute leukemia, hematopoietic stem cell transplantation, interferon- $\alpha$ , minimal residual disease, graft-versus-host disease

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## SUCCESSFUL TREATMENT OF CLASSICAL HODGKIN LYMPHOMA (HL) POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD) WITH PEMBROLIZUMAB AFTER FAILING BRENTUXIMAB

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**Case:** A 34-year-old man was diagnosed PTLD, morphologically HL mixed-cellularity(MC) subtype at 36th month after his second 10/10 matched unrelated donor(MUD) haematopoietic stem cell transplant(HSCT). He was first diagnosed with erythropoietic protoporphyria at age 21, and underwent first 10/10 MUD HSCT with Fludarabine/cyclophosphamide/TBI/ATG in Sept-2011. He remained free of porphyria attack post-transplant, had no chronic graft-vs-host-disease(cGVHD), and stopped all immune-suppressants one year post-transplant. But he was later diagnosed with therapy related acute myeloid leukaemia Nov-2013. After induction therapy, he achieved remission and underwent second non-myeloablative (no ATG) HSCT from another 10/10 MUD in Apr-2014. He remained in continued remission, but with mild cGVHD liver. There was fluctuating EBV viremia, which was kept under observation.

**Progress:** Then in Apr-2017, he developed two 1cm non-tender cervical lymph nodes. Excisional biopsy diagnosed PTLD-HL-MC, which was EBV associated, CD30 positive and CD20 negative. There was now persistent EBV viremia. PET-CT showed generalized hypermetabolic lymphadenopathy. Immuno-suppressants were quickly weaned off. He received 8 doses of Brentuximab. Interim PET-CT showed complete metabolic response. Serum EBV DNA fell initially but remained positive. Post-treatment PET-CT showed hypermetabolic retroperitoneal mass.

Treatment was changed to Pembrolizumab 100mg/dose. Serum EBV DNA became undetectable after third dose. PET-CT scan after sixth dose showed complete metabolic response. He received 8 doses of Pembrolizumab before switching to Nivolumab 40mg/dose, another programmed death 1 (PD-1) inhibitor, as maintenance due to cost concerns. At reporting, he had received 4 doses of Nivolumab. He remained asymptomatic, GVHD free, with undetectable serum EBV DNA.

**Discussion:** Immune-checkpoint blockade by anti-PD1 are effective in treatment of relapse refractory HL. Here, we report successful treatment of HL-PTLD. To our knowledge, this is the second reported case regarding use of anti-PD1 in PTLD. Concerns for GVHD flare calls for close monitoring.

**Keywords:** PTLD, Hodgkin, Pembrolizumab, EBV



## THE DEVELOPMENT OF ANTI-RO52 ANTIBODIES AFTER ALLOGENEIC STEM CELL TRANSPLANTATION IS RELATED WITH CHRONIC GRAFT-VERSUS-HOST DISEASE

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**Background:** Chronic graft-versus-host disease (cGVHD) is a major cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Donor CD4+ T and B cells play important roles in cGVHD pathogenesis. Donor B cell derived antibodies augment the development of bronchiolitis obliterans in a murine model of cGVHD. In this study, we analyzed the occurrence of autoantibodies in 120 patients surviving longer than 3 months after allo-HSCT to detect an association between occurrence of autoantibodies and development of cGVHD.

**Material and Methods:** A total of 120 patients with hematologic malignancies who underwent allo-HSCT at Nanfang Hospital between December 2014 and March 2018 were enrolled in this experimental study. Patients with cGVHD were closely matched to patients without cGVHD according to age, gender, stem cell source, conditioning regimen, GVHD prophylaxis and grade of acute GVHD. The diagnosis and grade of cGVHD were made at the time of sample collection according to National Institutes of Health criteria (Howard M.S. et. al. BBMT 2015). Comparison of categorical variables was performed on the chi-square test. Comparison of mean between two groups was performed on the student t-test. Among three groups comparison was used the one-way ANOVA. Comparison of cumulative incidence was using the log-rank test. All tests were two-sides and statistical significance was defined as P value of <0.05.

**Results:** Autoantibodies were not found in 48 of 50 patients without cGVHD (96%). Anti-Ro52 antibody and anti-histone antibody were detected in only two patients without cGVHD (2%) respectively. Autoantibodies were found in 44 of 70 patients with cGVHD (57%). Among these autoantibodies, anti-nuclear (ANA) were found in 33 patients (47%), anti-Ro52 antibody in 17 (24%), anti-histone antibody in 2 (3%), anti-mitochondrial antibody in 2 (3%), anti-ribosomal P protein antibody in 1 (1%), anti-histidyl tRNA synthetase antibody in 2 (3%), anti-polymyositis/scleroderma antibody in 2 (3%), anti-centromere B antibody in 1 (1%). ANA was more frequently detected in patients with cGVHD than patients without cGVHD ( $P < 0.05$ ) as well as anti-Ro52 autoantibodies ( $P < 0.001$ ). Subsequently, we found patients with cGVHD had 17.83-fold amounts of anti-Ro52 autoantibodies than patients without cGVHD. Higher levels of anti-Ro52 autoantibodies were detected in patients with moderate/severe cGVHD than patients without cGVHD ( $P < 0.05$ ). We also found ANA and anti-Ro52 autoantibodies significantly correlated to cGVHD and its severity. Patients who were detected anti-Ro52 autoantibodies within 6 months had subsequent impaired reconstitution of CD19+ B cells after 12th month from transplantation ( $P < 0.01$ ). We further found that patients with moderate/severe cGVHD had a

higher risk of developing anti-Ro52 autoantibodies than patients with mild cGVHD (80.76% vs 63.48%;  $P < 0.0001$ ) and patients without cGVHD (80.76% vs 2%;  $P < 0.0001$ ) at 30 months after transplantation.

**Conclusion:** These results demonstrate that patients with cGVHD significantly correlated with the autoantibodies, especially ANA and anti-Ro52 autoantibodies. Patients who had an elevated level of anti-Ro52 autoantibodies were more likely to develop cGVHD.

**Keywords:** Chronic Graft-versus-host Disease, anti-Ro52 Autoantibodies, Anti-nuclear Autoantibodies, Allogeneic Hematopoietic Stem Cell Transplant

## THE IMPACT OF DONOR FULL LENGTH KIR2DS4 IN THE DEVELOPMENT OF ACUTE AND CHRONIC GVHD AFTER UNRELATED ALLOGENEIC HSCT

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**Purpose or Background:** In this study we investigated the patients' overall survival (OS), relapse-free survival (RFS), relapse, incidence of CMV reactivation, and acute and chronic GVHD after unrelated donor HSCT in our hospital, and assessed the possible impact of donor KIR2DS4 allelic variants (full length or deleted) on these end points.

**Method or Case:** Retrospective cohort study

**Results or Progress:** KIR and HLA genotyping were determined in 75 pairs of Chinese pediatric hematologic malignancy patients. Among the 75 donor-recipient pairs, 77.3% (58/75) of the donors were positive for full length KIR2DS4, 22.7% (17/75) were negative. Multivariate analysis showed that a higher risk of aGVHD occurred when donors were positive for full length KIR2DS4 compared with donors who were negative for full length KIR2DS4 (HR=2.166, 95%CI: 1.01-4.26, P=0.0251). Subgroup analysis showed that AML and CML patients who received donors positive for full length KIR2DS4 have a higher cumulative incidences of cGVHD (62% vs 75%, P=0.008). There was no significant effects of full length 2DS4 on overall survival (P=0.13), relapse free survival (P =0.14), CMV reactivation (P=0.52) and relapse (P=0.39).

**Conclusion or Discussion:** Our findings indicated a significant correlation of donor full length KIR2DS4 on aGVHD and cGVHD for patients received unrelated donor HSCT, combining KIR and HLA genotyping could help make a better sense of transplants in these patients.

**Keywords:** NK cell, KIR2DS4, acute GVHD, chronic GVHD, allogeneic hematopoietic SCT

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## THE INFLUENCE OF CISPLATIN ADMINISTRATION BEFORE TRANSPLANTATION ON KIDNEY FUNCTION EARLY AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Background:** Cisplatin is included as a key drug for salvage treatment of malignant lymphoma. Renal dysfunction is often observed early after allo-HSCT, sometimes causing non-relapse mortality. It is unclear whether the use of cisplatin before allo-HSCT has adverse effects on post-transplant kidney function.

**Method:** This study is a post-hoc analysis of a prospective observational cohort study at our institute, which aimed at investigating the influence of cisplatin administration before HSCT on kidney function early after HSCT. Our cohort were patients who received HSCT between April 2017 and February 2019. Serum creatinine and serum cystatin C were measured at pre-HSCT, 30 days and 90 days after HSCT and the estimated glomerular filtration rate (eGFR) including eGFR<sub>cre</sub> and eGFR<sub>cys</sub> (mL/min/1.73 m<sup>2</sup>) was calculated.

**Results:** Eighty-eight patients were enrolled. Median age was 54.5 years (range, 19-68). Twenty-eight patients had malignant lymphoma, and 7 of them received cisplatin before HSCT (DLBCL: 1, FL: 2, PMBL: 1, PTCL: 3). Median total dose of cisplatin was 100 mg/m<sup>2</sup> (range, 75-375 mg/m<sup>2</sup>). At 30 and 90 days after HSCT, eGFR<sub>cys</sub> was significantly lower than eGFR<sub>cre</sub> (median: pre-HSCT 91.4 vs. 91.7, P=0.880; 30 days after HSCT 98.5 vs. 72.5, P<0.001; 90 days after HSCT 75.3 vs. 62.9, P<0.001). The administration of cisplatin was not associated with poor kidney function at pre-HSCT (median: eGFR<sub>cre</sub> 85.0 vs. 92.3, P=0.496; eGFR<sub>cys</sub> 82.7 vs. 93.0, P=0.508), but significantly reduced eGFR<sub>cys</sub> at 30 days after HSCT (median: 30 days after HSCT eGFR<sub>cre</sub> 79.7 vs. 99.2, P=0.074; eGFR<sub>cys</sub> 38.1 vs. 75.5, P=0.024; 90 days after HSCT eGFR<sub>cre</sub> 59.3 vs. 75.6, P=0.259; eGFR<sub>cys</sub> 40.3 vs. 64.5, P=0.077).

**Conclusion:** Use of cisplatin before HSCT was associated with an early decline in post-transplant kidney function determined by eGFR<sub>cys</sub>. Larger studies are warranted to further clarify the impact of pre-transplant use of cisplatin on the post-transplant clinical outcomes including renal failure.

**Keywords:** Renal dysfunction, Cisplatin, Cystatin C

## THE RETROSPECTIVE STUDY OF DEFIBROTIDE IN THE TREATMENT OF CHILDREN WITH SINUSOIDAL OBSTRUCTION SYNDROME AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Purpose or Background:** Sinusoidal obstruction syndrome(SOS), also known as hepatic veno-occlusive disease(VOD), is a leading cause of morbidity and mortality after hematopoietic stem-cell transplantation (HSCT) in children. Defibrotide is the only drug that has been proven to be effective in the treatment of SOS/VOD after HSCT

**Method or Case:** We retrospectively analyzed 25 children diagnosed with SOS/VOD after HSCT between 2000 and 2017 at the department of Hematology/Oncology in Shanghai Children's Medical Center. In this study, the Seattle criteria was used in the diagnosis of SOS/VOD, some delayed cases met the EBMT 2017 criteria.

**Results or Progress:** The morbidity of SOS/VOD in our center is 2.21%(25 in 1129 cases), and there were 14 patients received defibrotide for the treatment of SOS/VOD. Defibrotide was discontinued due to clinical improvement, death or economic factors. The median duration of defibrotide therapy was 11 days (3–48 days). Resolution of SOS/VOD (bilirubin < 2 mg/dl with improvement in other symptoms and signs) was seen in 10 patients (71%). The survival analysis demonstrated that the defibrotide therapy was significant correlated with high survival rate (78.6% vs. 9.1%,  $P < 0.01$ ). And no severe hemorrhage related to defibrotide administration was observed.

**Conclusion or Discussion:** Defibrotide is an effective and relatively safe treatment for children with SOS/VOD after HSCT.

**Keywords:** defibrotide, sinusoidal obstruction syndrome, hematopoietic stem-cell transplantation

## THE ROLE OF NESTIN + MESENCHYMAL STEM CELLS (MSCs) IN BONE MARROW CHRONIC GRAFT-VERSUS-HOST DISEASE

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**Background:** Chronic graft-versus-host disease (cGVHD) is a major cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT). cGVHD is a syndrome of variable clinical features resembling autoimmune, involving not only the epithelial target tissues (skin, lung, gastrointestinal tract and liver) but also any other organ system (musculoskeletal, oint, ocular and genital tissues). Bone marrow (BM) suppression without infection is often observed in patients undergoing allo-HSCT as GVHD symptoms appear, suggesting that BM could be a target of cGVHD.

**Method:** We used a murine model of cGVHD characterized by MHC-mismatched BALB/c (H-2d) recipients given C57BL/6 (H-2b) grafts. The alterations of BM environment between cGVHD and TCD-BM groups were detected at day 60 post allo-HSCT. The results were compared using unpaired two-tailed Student t-test. Statistical significance was defined as P value of < 0.05.

**Results:** We observed that BM displayed a significant increase in collagen and reticulin fibers deposition in cGVHD group compared to non-cGVHD group. The decreased absolute numbers of leukocytes, lymphocytes and red blood cells in the peripheral blood indicated the BM suppression in the cGVHD group. We further demonstrated that Nestin + MSCs located in BM niche underwent tremendous expansion in cGVHD group ( $P < 0.001$ ). Nestin+ MSCs in cGVHD group acquired expression of alpha smooth muscle actin (a-SMA). Besides, transforming growth factor- beta1 (TGF- $\beta$ 1) concentrations also increased in cGVHD BM microenvironment ( $P < 0.001$ ). High concentrations of TGF- $\beta$ 1 induced formation of nestin+ MSC clusters and more transition from Nestin+ MSC to a-SMA+ Cells ( $P < 0.01$ ). In addition, expanded Nestin+ MSC in cGVHD group were surrounded by more macrophages ( $P < 0.001$ ).

**Conclusion:** Nestin+ MSC participate BM cGVHD development through transition to a-SMA+ Cells induced by high TGF- $\beta$ 1 in cGVHD microenvironment.

**Keywords:** Allogeneic hematopoietic cell transplantation, Chronic Graft-versus-host disease, Bone marrow environment, Mesenchymal stem cell, Macrophage

## THE SUCCESSFUL TREATMENT WITH BORTEZOMIB IN TWO CASES OF REFRACTORY AUTOIMMUNE HEMOLYTIC ANEMIA AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Background:** Autoimmune hemolytic anemia (AIHA) is a late complication of allo-HSCT. In patients who had no response to corticosteroids and rituximab more commonly in the post allo-HSCT setting ,other immunosuppressive therapies often show unsatisfactory responses.

**Case1:** A 5-year-old Child with thalassemia major(TM) received an unrelated allo-HSCT which is M/F,O/B ABO mismatched, 10/10 matched with myeloablative conditioning. The patient developed to AIHA at day + 242 after HSCT. The analytical data were as follows: hemoglobin 41 g/L, LDH 585 IU/L, positive in direct and indirect Coombs test. She received of IVIg at 2 g/kg\*2, prednisone at 3mg/kg ,plasmapheresis aggressive and blood transfusion support,resulting in temporary stabilization of Hb .Over the next 4 months, other immunosuppressive therapies with cyclosporin A,cyclophosphamide, mycophenolate mofetil were unsatisfactory responses.8 weekly doses of rituximab at 375 mg/m<sup>2</sup> .She had persistent anemia and developed G + sepsis. At 5 months after first onset of hemolysis, she was started on bortezomib at 1.3 mg/m<sup>2</sup> subcutaneously at D1, 4, 8, and 11. The last RBC transfusion was given at 8 days after the first dose of bortezomib. She is now 12 months from the last dose of bortezomib and her Hb has remained normal.

**Case2:** A 4-year-old Child with TM,MUD-HSCT , M/F,A/B,10/10 matched .The patient developed to AIHA at day + 320 after HSCT. She received treatment with prednisone ,IVIg and rituximab 4 doses.She had persistent severe anemia. Bortezomib 1.3 mg/m<sup>2</sup> (8 doses) was gaved at 2 months.The hemoglobin rose to the normal level and the DAT became negative .

**Discussion:** Our cases provide additional evidence for the efficacy of bortezomib in refractory AIHA after HSCT. It is believed that bortezomib mediates depletion of plasma cells responsible for the persistent production of autoantibodies ,depletion of autoreactive T cells, suppression of inflammatory NF-kB signaling .

**Keywords:** Hematopoietic stem cell transplantation, Autoimmune hemolytic anemia, Thalassemia, Glucocorticoid, Rituximab, ;Bortezomib

## THE UTILITY OF RUXOLITINIB IN PATIENTS WITH CORTICOSTEROID-REFRACTORY GRAFT-VERSUS-HOST-DISEASE : SINGLE CENTER RETROSPECTIVE ANALYSIS

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**Purpose or Background:** Graft versus host disease (GVHD) causes significant morbidity and mortality in patients after allogeneic stem cell transplantation(allo-HSCT). JAK1/2 are critical for inflammatory cytokine response in GVHD. Ruxolitinib is a small molecule inhibitor of JAK1/2. Preliminary data indicated substantial clinical action in patients with corticosteroid refractory graft versus host disease(SR-GVHD).

**Method or Case:** This study enrolled 42 Chinese patients who had received ruxolitinib as salvage-therapy for SR-GVHD. Patients were classified as having SR-aGVHD (n=20, all grade III or IV) or SR-cGVHD (n=22, all moderate or severe). The efficacy of Ruxolitinib was evaluated at day 28 after the initial treatment. The associated factors of clinical outcome was analyzed. The tests were two-sided at a significance level of 0.05.

**Results or Progress:** At day 28 after starting ruxolitinib treatment, the overall response rates (ORR) was 60% (20% complete response [CR]) in SR-aGVHD, while for SR-cGVHD the ORR was 72.7% (9.09% CR). The 6-month overall survival (OS) was 59.6% (5.64%–58.16%,95%CI) and 81.3% (64.64%–97.96%,95%CI) for SR-aGVHD and SR-cGVHD, respectively. The median follow-up time was 21.6 (1~48) weeks, 6-month failure-free survival (FFS) was 40.0% (95%CI 21.86%~60.14%) in SR-aGVHD patients. While for SR-cGVHD patients, the median follow-up time was 35.1 (5~68) weeks, 6-month FFS was 81.3% (64.64%–97.96%,95%CI). The most common hematologic adverse events were anemia and thrombocytopenia, which were dose-dependent. Univariate analysis showed that grade IV aGVHD and NIH 3 cGVHD may indicate poor efficacy of ruxolitinib (ORR grade III vs IV 88.9% vs 36.4%, P=0.028; moderate vs severe 92.3% vs 44.4%, P=0.023).

**Conclusion or Discussion:** Ruxolitinib may constitute a promising new salvage treatment option for SR-GVHD that should be verified in a prospective trial and more clinical practice.

**Keywords:** Graft-versus-host disease, Ruxolitinib, Salvage therapy



## CLINICOPATHOLOGICAL OUTCOMES OF ALDH1 CANCER STEM CELL MARKER IN OVARIAN CANCER PATIENTS: EVIDENCE FROM A META-ANALYSIS

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**Background:** There is always a need for relevant biomarkers for ovarian cancer. Published studies found ALDH1 as a potential in the marker for cancer patients. However, the effectiveness of ALDH1 as a marker in ovarian cancer patients remains doubtful. So, this study aimed to understand the clinicopathological outcomes of ALDH1 in ovarian cancer patients.

**Method:** PubMed, Embase and Cochrane central databases were searched for the published studies assessing the impact of ALDH1 as a marker in ovarian cancer patients. Study search was performed by two independent investigator using suitable search terms. The search period was from inception to January 2019. The primary outcome was to assess the association of ALDH1 with the clinicopathological outcomes in ovarian cancer patients. Risk of bias was assessed using nonrandomized studies of interventions tool Overall survival was considered under secondary outcomes. RevMan v5.3 was used for the statistical analysis.

**Results:** A total of 15 studies were found to be eligible for the qualitative analysis, while few studies qualified for the quantitative analysis. Majority of the studies were of high quality. Random effect model was chosen over the fixed effect model because of the presence of significant heterogeneity. ALDH1 was found to be significantly associated with tumor stage (TNM stage) with a relative risk (RR) of 1.85 (95% CI: 1.11 to 3.10),  $p = 0.01$ . ALDH1 was also found to be significantly associated with the lymph invasion RR 2.76 (95% CI: 1.10 to 7.18),  $p = 0.03$ . ALDH1 was associated with the poor survival outcomes RR 1.47(95% CI: 1.22 to 1.86),  $p = 0.000$ .

**Conclusion:** ALDH1 was found to be a potential predictive stem cell marker for assessing the clinicopathological outcomes in ovarian cancer patients. However, further controlled studies are warranted.

**Keywords:** ALDH1, Biomarker, Cancer, Systematic Review, Meta-analysis

## FACTORS PREVENTING PARTICIPANTS FROM DONATING HEMATOPOIETIC STEM CELLS: A LITERATURE STUDY

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**Purpose or Background:** Stem cells have great potential for treating various diseases and conditions such as severe aplastic anemia, chronic myeloid leukemia, thalassemia, and sickle cell anemia. Hematopoietic stem cell donations (HSCD) can be from the bone marrow of a match family member or other unbound individual if family member don't match. However finding a compatible donor is very difficult, one reason is someone's reluctance to donate. This study aims to identify the factors that prevent individuals to donate hematopoietic stem cells to their families and non-bound individuals. Thus, it can help in recruiting more contributors.

**Method or Case:** The method used is to study several published journals. From several journals collected, 8 articles were selected.

**Results or Progress:** The results of this study found that several factors that prevented individuals from donating were lack of awareness that transplants could save lives, donations, opportunities, lack of information about HSCD and risks, fear of pain, health problems, worry about effects after donating, marital status (single) and lack of trust in the health system. There are no racial and religious differences in willingness to donate. Young participants are more likely to donate.

**Conclusion or Discussion:** The government and charitable organizations can consider developing a policy of providing subsidies to donor recipients and compensation to donors. Increasing knowledge about HSCD and its risks are important to do. In addition, better HSCD education can help overcome fear of pain. Regional blood donor centers are suitable for recruiting new donors because routine blood donors are more often informed about HSCD from health professionals. Then, the health system needs to be improved to increase the trust of donors.

**Keywords:** stem cell, hematopoietic, donate

## IMPACT OF CANCER STEM CELL MARKER CD44 ON CLINICOPATHOLOGICAL OUTCOMES AMONG OVARIAN CANCER PATIENTS

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**Background:** CD44 is considered as a potential diagnostic tumor marker. Previous published studies confirm the association of CD44 and its isoforms with the progression of epithelial ovarian cancer. However, clinicopathological outcomes and patients survival remains unclear. So, in this study, we aimed to assess the impact of CD44 marker on clinicopathological outcomes and on the survival of ovarian cancer patients.

**Method:** A Literature search was performed in PubMed, Embase, and other databases by an independent investigator. Only those studies qualified for inclusion which reported the clinicopathological outcomes. The primary outcome of this study was to investigate the association of CD44 marker on the clinicopathological outcomes of ovarian cancer patients. Secondary outcomes include overall survival response. All the analysis was done with RevMan software.

**Results:** This study was based on seventeen studies incorporating data for CD44s isoform and CD44V6 isoforms. All the included studies were of moderate to high quality as judged through risk of bias in nonrandomized studies of interventions tool. Random effect model was applied for the analysis because of the presence of significant heterogeneity. We found that CD44s overexpression is significantly associated with chemotherapy resistance with a relative risk of 3.14 (95%CI: 1.13 to 9.05),  $p = 0.02$ . No association was observed with the tumor grade and pathological type. Poor survival was observed for overexpression of CD44 in ovarian cancer patients with a pooled risk of 1.42 (95% CI: 1.04 to 2.05),  $p = 0.05$ .

**Conclusion:** CD44 cancer stem cell marker was found to be useful as a predictive and prognostic marker in ovarian cancer patients.

**Keywords:** Biomarker, Cancer, CD44, Prognosis, Stem cell, Meta-analysis

## MICRORNA-9: ROLE IN THE DEVELOPMENTAL DIFFERENCES OF HUMAN MEGAKARYOCYTES BY REGULATION OF RUNX1

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**Background:** Neonatal cord blood (CB) cells are promising alternatives to adult bone marrow (PB) in cellular therapies. CB cells have the potential to develop into specialized cells, such as erythrocytes or Megakaryocytes (MKs). MKs are responsible for the production of platelets, thrombocytopenia is a low platelet ( $<150 \times 10^9/L$ ) condition, which is common among sick infants. We hypothesize that developmental differences between CB- and PB-MKs contribute to the vulnerability of neonates to develop severe thrombocytopenia. Non-coding microRNAs (miRNAs) may play a critical role in the regulation of MK development as they have been shown to be involved in HSCs development and malignant transformation.

**Method:** To study the biological role of miRNAs in MK-development, human CB and PB derived CD34+ cells were cultured in the presence of thrombopoietin for 14 days. Cultures expressing  $>90\%$  CD41+ MKs by flow cytometry were collected and 88 miRNAs involved in HSCs development were examined. miRNA validation studies were performed in cell line models.

**Results:** The largest developmental difference was observed with miR-9 (22 fold) expression. Furthermore, RUNX1 has emerged as a putative target of miR-9 by several bioinformatic databases. RUNX1 sequence, which miR-9 binds to, is conserved among vertebrates, showing the functional significance of the miR-9/RUNX1 axis during evolution. We compared hsa-miR-9 expression levels at different time points during MK development and found a constitutively increased pattern of hsa-miR-9 expression through all stages of neonatal-MK development compared to adult, whereas RUNX1 expression was significantly lower in neonatal-MKs as compared to adult. miR-9/RUNX1 axis was confirmed by pre-miR-9 transfection study in Meg01. Interestingly, increased cell proliferation with reduced RUNX1 expression was observed in pre-miR-9 transfected cells as compared to control.

**Conclusion:** The present study shows the functional significance of miR-9 in RUNX1 regulation, which may contribute to the developmentally different and disease susceptible phenotype of neonatal MKs. Therefore, it could be a potential target in neonatal thrombocytopenia and other platelet disorders.

**Keywords:** Megakaryocyte, Thrombocytopenia, miRNA, Runx1, Platelets

## NARINGENIN-LOADED MODIFIED POLYCAPROLACTONE NANOPARTICLES PROTECTS HUMAN MESENCHYMAL STEM CELLS FROM OGD-INDUCED HYPOXIA VIA ATTENUATING INFLAMMATION

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**Purpose or Background:** Ischemic stroke (IS) is brain damage instigated by partial/complete interruption of blood supply to the brain. Inflammation is involve in the disease mechanism of ischemic stroke due to production of pro-inflammatory mediators. Stem cell based therapy has promising potential for the treatment of ischemic stroke. Human mesenchymal stem cells (MSCs) are being widely used for the treatment of ischemic stroke but low survival rate of post-transplanted stem cells remains a challenge. Therefore, in this study, we evaluated effects of naringenin-loaded gelatin-coated polycaprolactone nanoparticles to protects MSCs against oxygen glucose deprived (OGD) insult. Naringenin reported to have strong anti-inflammatory property and thus selected as a drug of choice for this study. Naringenin has very low aqueous solubility and efficient delivery remain challenges for naringenin.

**Method or Case:** The present study showed that inflammation occurred in MSCs during their treatment with oxygen glucose deprivation (OGD) and was well reversed by treatment with naringenin-loaded gelatin-coated polycaprolactone nanoparticles.

**Results or Progress:** Briefly, the results of this study indicated that naringenin-loaded gelatin-coated polycaprolactone nanoparticles were able to protect the loss of cell membrane integrity and neuronal morphology. Naringenin-loaded gelatin-coated polycaprolactone nanoparticles exerted protective effects onto the human MSCs against OGD-induced inflammation as shown by decreased pro-inflammatory cytokines (TNF- $\alpha$ , IFN- $\gamma$ , and IL-1 $\beta$ ) levels and other inflammatory biomarkers (COX2, iNOS, and MPO activity).

**Conclusion or Discussion:** Naringenin-loaded gelatin-coated polycaprolactone nanoparticles have potential to be used as adjunct therapy along with stem cells as it provide anti-inflammatory effects and thus have potential to improve MSC-based therapy. Our naringenin-based nanoformulation may have a wide therapeutic application in ischemic stroke and other neuro-inflammatory diseases.

**Keywords:** Human Mesenchymal Stem cells, Inflammation, Naringenin, Nanoparticle

## STEM CELL THERAPY IN CANCER PATIENT IN SEVERAL HOSPITALS IN INDONESIA

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**Background:** Stem cell therapy is one of many therapies used to repair cardiac infraction and to regenerate cardiac cell. Since the discovery of existing highly potential cells within our body, stem cell become a new phenomena that bring us hope in finding the cure for many disease, especially disease that require cellular regenerative properties to form new tissue or organ. The ability of stem cells that can form tissue or organ make scientists put high expectation for the outcome of this program. The further we known about stem cell, it is realized that stem cell existed within tumor mass (Cancer Stem Cell or CSC). The aim of this study is to know the potential of stem cell therapy in cancer patient in several hospitals in Indonesia.

**Method:** Data obtained from secondary data on 12 articles selected published journal that have been carried out in the last 10 years (2009-2019), with sample is cancer patients conducted in several hospitals in Indonesia.

**Result:** The result showed that CSC, currently supported are found in humans by using methods on normal stem cells. The discovery of cancer stem cells and their characteristics brings new hope in determining the prognosis of recurrence and cancer therapy. The discovery of new anti-cancer therapies targeted specifically is differentiated and inactive cancer cells guided by SCS gene markers in the treatment process, expected to increase the rate of improvement in the treatment.

**Conclusion:** It can be concluded that stem cell therapy is a potential treatment to provide greater life expectancy for cancer patients in Indonesia. It is believed that if we could eradicate the cancer stem cells we may find that we are one step closer into finding the cure for cancer. This knowledge then leads into efforts finding better approach to the treatment.

**Keywords:** Stem Cell, Cancer, Cancer Stem Cells, Indonesia

## STUDY ANALYSIS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION PROBLEMS IN INDONESIA

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**Purpose or Background:** The hematopoietic stem cells (HsCs) are stem cells that have the role of producing mature blood cells in the body. HsCs are found in the spinal cord, peripheral blood and cord blood. In Indonesia, HsCs have been developed by Indonesia Allogeneic BMT, but were stopped due to lack of patients and limited to the upper class. It is different from Singapore and Malaysia with advanced economies capable of providing services from various circles.

**Method or Case:** This study used electronic data as a method by reviewing some previous article published

**Results or Progress:** The results showed that the problem of HsCs was first, post-transplant side effects, such as chronic Graft versus Host Disease (GVHD), secondly, complications of HSCT carried out in other countries, third, unhealthy commercial market services, and fourth, the cord blood stem cell banking from foreign countries offered to pregnant parents

**Conclusion or Discussion:** Indonesia needs to revive its own HSCT program, so that this program can serve and be protected by Indonesian law

**Keywords:** hematopoietic stem cell Transplantation problems, GVHD, Indonesia

## ALLOGENEIC STEM CELL TRANSPLANTATION FOR PRIMARY IMMUNODEFICIENCY DISORDERS: AN EXPERIENCE FROM INDIA

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**Purpose or Background:** Allogeneic Hematopoietic stem cell transplant (HSCT) is a curative option for a many types of primary immunodeficiency disorders (PID). Here we describe our experience of allogeneic HSCT for PID in children

**Method or Case:** We retrospectively analyzed data of 18 children (mean age 5 yr. +/- SD-4.92 and male/female-5:1) suffering from PID from two centers treated between April 2013 to April 2019. The diagnosis of were hemophagocytic lympho-histiocytosis-28%, Wiskott-Aldrich Syndrome-22%, Severe combined immune deficiency-17%, Heme-Oxygenase-1 Deficiency-13% and others-20%. Conditioning regimen used was serotherapy based in all except 1 case. Conditioning was myeloablative in 4 and reduced intensity in 13 patients (Fludarabine, Cyclophosphamide, Total body irradiation 2 Gy was used in 8) and no conditioning in 1. The stem cell source was peripheral blood stem cells-67%, bone marrow-28% and cord-5%. Type of transplant was haploidentical donor-67%, matched related donor-23 %; matched unrelated donor-5% and unrelated cord-5%. Graft vs. Host Disease (GVHD) prophylaxis in haploidentical HSCT was post-transplant cyclophosphamide (PTCy) in 12 patients and TCR alpha-Beta depletion in 1. In matched related it was Tacrolimus and Mycophenolate in 3 and Cyclosporine & Methotrexate in1. In cord blood it was cycloporine and methyprednisone in 1.

**Results or Progress:** Fourteen patients engrafted (neutrophils mean 17.07 +/-3.65 days, platelet mean 15.57 +/-4.62 days). Four patients died prior to engraftment (2 with sepsis both were on ventilator before HSCT and 2 with rejection). The mean cell dose was 14 million/kg. The chimerism was fully donor in 13/14 patients and stable mixed chimerism in 1/14. At Day 100; 78 % patients continued to be disease free. Three patients died after day 100 due to renal failure-1, liver GVHD-1 and sepsis-1. Eleven patients (61%) are alive and disease free at median follow-up of 4 +/- 2.18 years. Overall incidence of acute GVHD was 33 % (all were grade I-II). Overall incidence of chronic GVHD was 17% (3/18) all of which 2 were limited and 1 was severe. Overall survival (OS) was 100% for matched related donor, 50% for haploidentical and 50% for unrelated donor/cord. OS was 75% for myeloablative and 62% for reduced intensity conditioning.

**Conclusion or Discussion:** Primary immunodeficiency disorders are curable with allogeneic HSCT. However, sepsis and rejection remain major hurdles in improving outcomes.

**Keywords:** Primary immunodeficiency disorders, Allogeneic Hematopoietic stem cell transplant, Outcomes



## BUSULFAN/FLUDARABINE-BASED OR TBI/FLUDARABINE-BASED REDUCED INTENSITY CONDITIONING REGIMENS IN HAPLOIDENTICAL STEM CELL TRANSPLANTATION FOR ACUTE LEUKEMIA

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**Purpose or Background:** To investigate the safety and efficacy of busulfan/fludarabine-based or TBI/fludarabine-based reduced intensity conditioning (RIC) regimens in haploidentical hematopoietic stem cell transplantation (HSCT) for the patients with acute leukemia.

**Method or Case:** From January 2018 to May 2019, 62 consecutive patients with acute leukemia (acute myeloid leukemia 27, acute lymphoblastic leukemia 32, and mixed phenotype acute leukemia 3) who underwent haploidentical HSCT with either busulfan/fludarabine-based or TBI/fludarabine-based RIC regimens were analyzed retrospectively. The median age was 15 (1-54) years old. Disease status included first complete remission (CR1) (24.2%),  $\geq$ CR2 (54.8%), and non-remission (21.0%). Busulfan: 3.2 mg/kg iv, 3 days; fludarabine: 30mg/m<sup>2</sup>, 5 days; TBI: 4Gy, 3Gy, 3Gy; ATG-F 5mg/kg, 4 days; Me-CCNU: 250mg/m<sup>2</sup>, 1 day. Cyclosporine, short-term MTX and mycophenolate mofetil were used for GVHD prophylaxis.

**Results or Progress:** All patients achieved durable engraftment. The incidences of grade II-IV and grade III-IV aGVHD were 29.0%, 16.1%, respectively. The incidence of cGVHD was 33.8%. The incidences of CMV and EBV reactivation were 21.0% and 12.9%, respectively. Hemorrhage cystitis occurred in 33.9% cases and all of them was in grade I or II. Fifteen patients died from GVHD (n=5) or relapse (n=10) and non-relapse mortality (NRM) was 8.1%. With the median follow-up 258 (35-511) days, overall survival (OS) and leukemia-free survival (LFS) were 75.8%, 71.0%, respectively.

**Conclusion or Discussion:** With current RIC regimens, our haploidentical HSCT for acute leukemia has shown excellent safety and efficacy with low incidences of aGVHD, cGVHD, NRM and viral reactivation, and high OS and LFS. Long-term follow-up is warranted.

**Keywords:** haplo-identical, fludarabine, cyclophosphamide, hematopoietic stem cell transplantation, reduced intensity

## CLINICAL EFFICACY OF HAPLOID TRANSPLANTATION WITH BU/CY/MEL PRETREATMENT SCHEME TO IMPROVE 40 CASES OF UNICENTRIC REFRACTORY RECURRENT ACUTE MYELOID LEUKEMIA

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**Purpose or Background:** At present, allogeneic hematopoietic stem cell transplantation is an effective radical treatment for refractory recurrent leukemia, which has poor chemotherapeutic effect and low long-term survival rate. How to Improve the Curative Effect by Modified Pretreatment Scheme? In this study, 40 patients with refractory relapsed acute myeloid leukemia are followed up by modified Bu/Cy/Mel regimen.

**Method or Case:** Select 23 children (< 14) and 17 adults with AML admitted to our hospital from March 2015 to June 2019, male: female = 30:10, median age: 9.5 years (1-63 years), there were 6 cases of M7, 22 cases of CR1 before transplantation, 4 cases of CR2/CR3, 4 cases of PR and 10 cases of NR1, the median number of leukemia cells before transplantation in PR and NR patients: 7.36% (1.2%-92%), transplantation type: 40 cases of haploid, donor stem cell sources: 31 cases of parents, 4 cases of brothers, offspring: 5, patient matching: 32 cases of HLA 5/10, 8 cases of HLA 6/10, stem cell sources: BM+PBSC, median of infused MCN:  $14.57 \times 10^8/\text{kg}$ , median of CD34 + cells:  $7.81 \times 10^6/\text{kg}$ , median of CD3 + cells:  $3.07 \times 10^8/\text{kg}$ , third-party cells: 38 cases of MSC, 2 cases of haplotype bone marrow, pretreatment scheme: Bu/Cy/Mel, 40 cases.

GVHD prophylaxis: CsA+MMF+sMTX, 40 cases of ATG-F i.e. Funing, with the dose of 7.5mg/kg

**Results or Progress:** The median follow-up time is 11.5 months (6-42 months), stem cells are implanted in 39 cases, except 1 case died on +6d. Median days of leukocyte engraftment were 15 (10-25), median days of platelet engraftment were 11 (4-51), and one case died of TRM pretreatment-related death.

Overall survival rate(OS): 77.5%, including EFS of CR1: 100%, CR2/CR3/CR4 50%, PR 50%, NR 50%. There are 9 deaths, 1 died of infection, 2 died of GVHD and 6 died of recurrence. All the 6 cases who relapse after transplantation are NR patients (6/40) and died. aGVHD-II-IV degree is 30%, III-IV degree is 20%, the incidence of cGVHD is 27.5%, hemorrhagic cystitis is 30%, CMV is 17.5%, EBV is 2.5%, and infection is 37.5%. No TMA, DAH and PTLD.

**Conclusion or Discussion:** Modified Bu/Cy/Mel pretreatment regimen will not increase the pretreatment-related mortality, but can significantly improve the efficacy of haploid transplantation and the long-term survival rate of refractory relapsed leukemia. It is a feasible regimen for the treatment of malignant relapsed leukemia, but requires a multi-center clinical research with large sample.

**Keywords :** transplantation, leukemia, AML, relapse, regimen, GVHD

## CLINICAL OUTCOME OF HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR HEMATOLOGIC MALIGNANCIES; A SEVEN YEAR FOLLOW UP STUDY FROM IRAN

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**Purpose or Background:** To explore the clinical outcome of human leukocyte antigen (HLA)-mismatched/haploidentical hematopoietic stem cell transplantation (HSCT) for patients with hematologic malignancies.

**Method or Case:** Clinical data of 85 patients who received HLA-mismatched/haploidentical HSCT following conditioning regimen comprised of busulfan/cyclophosphamide (BU/CY) plus thymoglobulin (ATG) from July 2010 to September 2017 were analyzed retrospectively.

**Results or Progress:** Of the 85 patients, 53 suffered from acute myeloid leukemia (AML), 29 had acute lymphoid leukemia (ALL), and 3 were diagnosed with other hematologic malignancies. At the time of transplantation 31 were in the first complete remission (CR1), 38 in second complete remission (CR2), 12 in third or more complete remission (CR3+) and the rest were primary induction failure cases. With a median follow-up of 18.8 months, 44 cases (52%) survived and 17 (20%) relapsed. The incidence of acute GVHD was 64.71% and chronic GVHD developed in 28.24% of patients. The estimated 3-year overall survival (OS) and disease-free survival (DFS) rate was 46.7% and 43.1%, respectively. Median 3-year DFS but not OS rate was significantly higher for AML patients than for ALL patients ( $P = 0.004$ ). Median 3-year OS but not DFS probabilities for male patients were higher than female patients ( $P = 0.045$ ). Prophylactic donor lymphocyte infusion (DLI), age, donor type (sibling vs other-related), and disease status at the time of transplantation were not independent factors affecting OS, DFS.

**Conclusion or Discussion:** Our results suggest that haploidentical HSCT could be a viable option with a reasonable OS and DFS when a full match donor is not available.

**Keywords:** haploidentical HSCT, outcome, hematologic malignancy

## CYCLOPHOSPHAMIDE FOLLOWED BY INTRAVENOUS BUSULFAN (CY-BU) AS MYELOABLATIVE CONDITIONING: IMPACT ON SINUSOIDAL OBSTRUCTION SYNDROME AND TRANSPLANT OUTCOMES, REAL WORLD EXPERIENCE

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**Purpose or Background:** Busulfan (BU) followed by Cyclophosphamide (BU-CY) is conventionally used conditioning regimens in allogeneic Hematopoietic Stem Cell Transplant (HSCT). The regimen has been associated with higher rates of Sinusoidal Obstruction Syndrome (SOS). Reversal of the protocol i.e cyclophosphamide followed by Busulfan (CY-BU) has recently been shown to reduce the rates of SOS.

**Method or Case:** We retrospectively analysed patients, who received CY-BU conditioning from Jan 2015 to Dec 2018, for effect on SOS and overall D100 mortality and morbidity. SOS was defined as per Baltimore criteria.

**Results or Progress:** Twenty nine patients underwent HSCT with a CY-BU conditioning. They were compared with 56 controls that underwent HSCT with BU-CY.

The median (IQR) age of patients was 17.5 (6.75 -35.25) years for BU-CY and 14.00 (6.00 - 27.00) years for CY-BU.

The diagnosis in both the groups combined were 13 (15%) ALL, 25 (29%) AML, 14 (17%) CML and 33 (39%) Thalassemia and others.

The median peak serum bilirubin in the CY-BU cohort was 1.4mg/dl as compared to 2.45mg/dl in the BU-CY cohort ( $p = 0.004$ ) and there was also a trend towards lesser transaminitis in the CY-BU group.

10% patients in the CY-BU group developed mild SOS in comparison to 25% in the BU-CY cohort. The incidence of severe SOS was 20% in the BU-CY group as compared to 3% in the CY-BU group. The p value for chi square test for overall difference in VOD between both the groups was 0.03.

There was no difference in occurrence of GVHD or other regimen related toxicity. There was no difference in the D+100 mortality in the two groups (14% (BU-CY) vs 17% (CY-BU),  $p = 0.72$ ).

**Conclusion or Discussion:** This study, limited by smaller number of patients, shows trend towards significantly less incidence of severe SOS and mortality due to SOS with CY-BU regimen.

**Keywords:** CY-BU conditioning, BU-CY conditioning, Stem Cell Transplant, Sinusoidal Obstruction Syndrome

## EARLY TAPERING OF IMMUNOSUPPRESSIVE DRUGS AFTER HAPLO-IDENTICAL TRANSPLANTATION IN PATIENTS WITH HIGH RISK LEUKEMIA

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**Purpose or Background:** Disease recurrence is the most important obstacle to achieve long-term survival for patients with advanced acute leukemia after allogeneic hematopoietic stem cell transplantation (HSCT). Several studies showed that early tapering of immunosuppressive agents could achieve graft versus leukemic (GVL) effects at early time after transplantation and the relapse most occurred at the first 6 months after transplantation. In order to reduce the relapse risk and improve the survival, the strategy of early tapering of immunosuppressive agents was retrospectively evaluated in haplo-identical stem cell transplantation patients with high risk leukemia.

**Method or Case:** Thirty patients with advanced leukemia received early tapering of immunosuppressive drugs between days 30 and 60 after HSCT according symptoms and signs with no grade II~IV acute or significant chronic graft versus host disease (GVHD).

**Results or Progress:** At the time of transplantation, 21 patients reached first or subsequent complete remission (n=15 for CR1, n=6 for CR2). The other 9 patients were non-CR or refractory to salvage therapy. Median time to stop immune-suppressants was 66 days after HSCT (32~98 days). Acute GVHD ± chronic GVHD was developed in 13 patients (43.3%) at median 27 days (13~113) after stopping immunosuppressive drugs. Only 3 patients had chronic GVHD with limited grade. During median follow-up duration (15.3 months), overall survival was 54.5% (58% in CR vs 50% in non-CR or refractory, P=0.777). Twelve patients (40%) died during the follow-up period and relapse was the most frequent cause of death (n=8, 26.7%). Other causes included secondary cancers (n=2) and acute GVHD (n=1), and fungal infection (n=1). In multivariate analysis, risk group based on cytogenetics and CMV reactivation was an independent prognostic factor for better survival; acute and chronic GVHD tended to be associated with better survival.

**Conclusion or Discussion:** In patients with high risk acute leukemia, the strategy of early tapering of immunosuppressive agents may facilitate post-transplantation strategies for relapse reduction and can lead to improve survival after allogeneic stem cell transplantation from haplo-identical donor.

**Keywords:** allogeneic stem cell transplantation, haploidentical donor, high risk leukemia, immunosuppressive drug

## EFFECT OF PRECONDITIONING REGIME FOR A BONE MARROW TRANSPLANTATION ON THE BONE MARROW EXTRACELLULAR MATRIX AND MODULATION POTENTIAL OF TONSIL-DERIVED MESENCHYMAL STEM CELLS

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To treat hematologic malignancies, high dose chemotherapy is still inevitably needed before bone marrow transplantation (BMT). Though busulfan and cyclophosphamide combination (Bu/Cy) is one of the typical preconditioning regimes, the effect of Bu/Cy on BM extracellular matrix (ECM) is not fully understood. BM-ECM modulation is one of the important steps for successful BMT. It was reported that co-transplantation of mesenchymal stem cells (MSCs) promotes BMT efficacy. In this study, we hypothesized that MSC secretions could modulate BM-ECM and BMCs homing. First, we treated BALB/c mice (n = 6/group) with Bu (20 mg/kg/day, 4 days) and Cy (100 mg/kg/day, 2 days) and after next day mouse were sacrificed and confirmed that Bu/Cy treatment increased ECM-related genes, especially Col4a1 and Col4a2, using targeted PCR array of ECM and adhesion molecules. Next, we validated type IV collagen expression by RT-PCR and immunohistochemistry. Col4a1 and Col4a2 were upregulated and Collagen IV was more detected in femurs of Bu/Cy-treated group than control group. We then investigated recovery effect of conditioned medium (CM) from tonsil-derived MSC by transwell migration assay in the presence or absence of collagen IV barrier, treating CM collected from 105 T-MSCs. We found that treatment of T-MSC CM improved rate of BMCs migration. In summary, increase in collagen IV deposition was observed after Bu/Cy treatment and inhibitory effects of type IV collagen on BMCs homing was resolved by T-MSC CM treatment. These data suggest that understanding of BM-ECM after high dose chemotherapy and T-MSC CM potential on modulation of BM-ECM would help to establish the more effective therapeutic strategies for BMT.

**Keywords:** bone marrow extracellular matrix, tonsil-derived mesenchymal stem cell, type IV collagen, preconditioning regime, bone marrow transplantation, BMC homing

## ESTIMATION OF OPTIMAL DONOR POOL SIZE FOR THE JAPAN MARROW DONOR PROGRAM (JMDP)

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**Purpose:** Unrelated hematopoietic stem cell donors with 8/8-allele match at HLA-A, -B, -C, and -DRB1 loci remain as the first alternative donor source for patients without HLA-matched siblings, and 7/8-matched donors can be selected in case where a 8/8-matched donor cannot be found because of their unique HLA haplotype. At present, the JMDP stands at more than 500,000 volunteer donors (exclusively Japanese) and continues to grow; however, its optimal donor pool size and composition remains to be elucidated. This estimation is crucial in JMDP as our society is rapidly aging.

**Method:** In considering an optimal donor registry size, we assessed the availability of 7/8-matched donors as well as 8/8-matched donors. We first constructed 5 sets of virtual 3,000 patient cohorts and donor pools of various sizes with simulated haplotype composition based on reported haplotype frequencies in Japan. Then we evaluated the probability with which patients have 8/8-matched or 7/8-matched donors in the simulated donor pool.

**Results:** The probabilities of finding five or ten candidates of 8/8-matched donors are 33% or 26% in 200,000 donors, 38% or 30% in 300,000 donors, 43% or 35% in 500,000 donors, respectively. These probabilities are almost same when candidate donors were restricted to those with identical haplotypes. In contrast, when HLA 7/8-matched donors are included to the analysis, higher probabilities of finding donors are estimated, with 45% or 36% in 200,000 donors, 51% or 41% in 300,000 donors, 58% or 48% in 500,000 donors, respectively.

**Conclusion:** Probability of finding multiple donor candidates substantially increases if 7/8-matched unrelated donors are considered as alternative donor candidates. The findings indicated that present donor pool size might be adequate. Further estimation of optimal donor pool size should also consider donor retention rates, the utilization rate of cord blood units and haplo-identical related donors.

**Keywords:** donor pool, unrelated hematopoietic stem cell transplantation, Japan Marrow Donor Program (JMDP)

## EXCELLENT OUTCOMES OF SECOND ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH REDUCED INTENSITY CONDITIONING REGIMENS IN ACUTE LEUKEMIA

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**Purpose or Background:** To evaluate safety and efficacy of reduced intensity conditioning (RIC) regimens in second allogeneic hematopoietic stem cell transplantation (allo-HSCT).

**Method or Case:** Between April 2018 and May 2019, 10 patients with leukemia (AML 6; ALL 4) who underwent second allo-HSCT were enrolled. They all failed to the first myeloablative allo-HSCT (haploidentical 9, unrelated 1) due to relapse (n=9) or secondary engraft failure (n=1). The median age was 25.5 (9–40) years old. Nine patients were in CR and one with relapsed disease before second transplant. The median interval between the first and second allo-HSCT was 13.5 (8–42) months. Different donors were used for the second allo-HSCT (haploidentical 6, unrelated 4). RIC regimens (TBI/Flu 9; Bu/Flu 1) were used for the second allo-HSCT. TBI: 4Gy, 2 days; fludarabine: 30mg/m<sup>2</sup>, 5 days; cytarabine: 1g/m<sup>2</sup>, 3 days; ATG-F 4mg/kg, 4 days; Me-CCNU: 250mg/m<sup>2</sup>, 1 day. One patient received the same conditioning except using busulfan (0.8mg/kg iv, q6h, 3 days) substituted for TBI due to his first HSCT with TBI containing regimen.

**Results or Progress:** The median time for neutrophil recovery was 14 (12–18) days, and the median time for platelet recovery was 15 (13–28) days. Nine patients became full donor chimerism, and one case who gave up early after second transplant due to financial issue could not be evaluated for chimerism and died from infection. The incidences of aGVHD, cGVHD were 11.1%, 33.3%, respectively. CMV and EBV reactivation was in 1/10 and 3/10 patients. One-year relapse rate and non-relapse mortality (NRM) were 0%, 10%, respectively. With a median follow-up of 8 (2.5–13) months, 9/10 patients were in MRD negative survival.

**Conclusion or Discussion:** Our RIC regimens have shown excellent safety and efficacy in second allo-HSCT in acute leukemia with low incidences of aGVHD, cGVHD, NRM and CMV reactivation and high disease-free survival. Long-term follow-up is warranted.

**Keywords:** RIC regimens, allo-HSCT, second, acute leukemia



## HAPLOIDENTICAL HEMATOPOIETIC CELL TRANSPLANTATION FOR SEVERE ACQUIRED APLASTIC ANEMIA: A NESTED CASE-CONTROL REGISTRYBASED COMPARISON STUDY OF POST-TRANSPLANT CYCLOPHOSPHAMIDE INCLUDED REGIMEN VS ANTI-THYMOCYTE GLOBULIN & COLONY-STIMULATING FACTOR -BASED REGIMEN

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**Purpose or Background:** In China, haploidentical allogeneic hematopoietic stem cell transplantation (haplo-HSCT) for severe aplastic anemia (SAA) involves anti-thymocyte globulin (ATG)/granulocyte colony-stimulating factor (G-CSF)-based protocol. The post-transplant cyclophosphamide (PTCY) regimen has emerged as an alternative strategy. We retrospectively compared the outcomes of SAA patients who had received these two regimens.

**Method or Case:** For each of 20 patients receiving PTCY regimen, 4 patients were randomly selected from patients receiving ATG/G-CSF regimen.

**Results or Progress:** The PTCY group showed delayed myeloid engraftment (16 days (range: 13-20 days) vs. 12 days (9-31 days),  $P < 0.001$ ), similar platelet engraftment (20 days (range: 11-36 days) vs. 16 days (range: 7-66 days),  $P=0.212$ ), comparable cumulative incidence of myeloid engraftment (100% vs.  $96.3 \pm 0.06\%$ ,  $P=0.081$ ), platelet engraftment ( $90.0 \pm 0.62\%$  vs.  $93.8 \pm 0.08\%$ ,  $P=0.473$ ) and GF ( $5.6 \pm 0.31\%$  vs.  $2.5 \pm 0.03\%$ ,  $P=0.556$ ). The PTCY group was comparable to the ATG/G-CSF group in overall survival ( $89.1 \pm 7.30\%$  vs.  $88.5 \pm 3.60\%$ ,  $P=0.972$ ; HR=0.46 (0.07-3.03),  $P=0.422$ ) and failure free survival ( $83.8 \pm 8.60\%$  vs.  $87.3 \pm 3.80\%$ ,  $P=0.679$ ; HR=1.46 (0.311-6.86),  $P=0.630$ ). Neither study group showed superior GVHD prevention. The CIs of grades II-IV aGVHD in PTCY and ATG/G-CSF group patients were  $15.0 \pm 0.68\%$  vs.  $32.5 \pm 0.28\%$  ( $P=0.111$ ), and of cGVHD were

27.9±3.07% vs. 20.7±0.23% (P=0.699).

**Conclusion or Discussion:** With faster myeloid engraftment, the ATG/G-CSF regimen in SAA patients receiving haplo-HSCT is potentially superior to the PTCY haplo-HSCT regimen. Prospective randomized controlled studies are required.

**Keywords:** aplastic anemia, haploidentical, transplantation, cyclophosphamide, ATG

## HAPLOIDENTICAL STEM CELL TRANSPLANTATION WITH POST TRANSPLANT CYCLOPHOSPHAMIDE FOR RELAPSED METASTATIC RETINOBLASTOMA.

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**Purpose or Background:** Outcomes of relapsed metastatic retinoblastoma are poor. Haploidentical donor hematopoietic stem cell transplant (HSCT) with post-transplant cyclophosphamide (PTCy) is a safe and effective therapy for leukemia and lymphoma. This same platform may provide graft vs. tumor effect in metastatic solid tumors like retinoblastoma leading to cure. We here report first and only case of a child with relapsed metastatic retinoblastoma who underwent haploidentical HSCT with PTCy.

**Method or Case:** A 3-year-old boy was diagnosed with localized retinoblastoma, Group D of left eye and initially treated with 12 cycles of Carboplatin, Vincristine and Etoposide as parents refused enucleation. He achieved complete remission (CR). However, he relapsed locally in left eye at the age of 5 years and underwent enucleation of left eye. Histopathology revealed poorly-differentiated retinoblastoma with disease beyond lamina cribrosa but optic nerve margin was clear. This was followed by external beam radiotherapy 40 Gy in 20 fractions. He remained asymptomatic for 10 months after which he developed pain in right upper abdomen. The imaging showed multiple FDG avid lesions in the liver, with largest lesion measuring 2x1.9 cm in segment V of liver. He had no local recurrence in left orbit and cerebro-spinal fluid was clear for malignant cells. The FNAC of one of these liver lesions showed metastatic malignant round cell tumor consistent with metastatic retinoblastoma. Bone marrow showed infiltration by the tumor. He was then treated as per HEADSTART 2A protocol with 5 cycles of cisplatin, cyclophosphamide, etoposide-based chemotherapy and he achieved CR2. After this child underwent haploidentical HSCT from father as donor after informed consent of the parents.

**Results or Progress:** Child was conditioned with cisplatin 50 mg/m<sup>2</sup> on day-7 added to original John Hopkins Haploidentical protocol (fludarabine, cyclophosphamide, TBI 2 Gy). Peripheral blood stem cells CD34 cell dose was 16.66million /kg) were given from father as donor. Graft vs. Host Disease (GVHD) prophylaxis was PTCy 50 mg/kg/dose on Day+3 and +4, mycophenolate mofetil and tacrolimus from day+5. His neutrophils engrafted on day 21 and platelets on day 14. He was discharged on Day +21. On Day +26, he developed acute GVHD grade I. He didn't get chronic GVHD. He was fully donor on Day +30 , 60 and 100. PET-CT scan done on day +55 showed no FDG avid disease. By day + 90 his immunosuppression was tapered off. His CXR and Ultrasound was normal on day +112. He continued to be well until Day +168 when he developed severe headache. MRI brain showed meningeal enhancement and multiple brain metastasis. PET CT scan showed no disease anywhere except in brain. Child received palliative radiotherapy for central nervous system (CNS) relapse but finally succumbed to his disease 6-months later.

**Conclusion or Discussion:** Haploidentical HSCT with PTCy can be performed safely for relapsed metastatic retinoblastoma. However, additional therapy might be needed to prevent CNS relapse post HSCT.

**Acknowledgements:** My deepest appreciation to Mr. Indra Bhushan Pandey who provided necessary information about patient possibly to complete this report.

**Keywords:** Haploidentical stem cell transplantation, Relapsed metastatic retinoblastoma, Post-transplant cyclophosphamide

## HAPLOIDENTICAL STEM CELL TRANSPLANTATION WITH POST TRANSPLANT CYCLOPHOSPHAMIDE IN PEDIATRIC MALIGNANCIES AND POST-TRANSPLANT IMMUNOMODULATION-IMPROVING OUTCOMES WITH COST-EFFECTIVE CARE IN DEVELOPING COUNTRIES

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**Background/Objectives:** Relapse is the main cause of mortality in haploidentical hematopoietic stem cell transplantation (HSCT) with post-transplant cyclophosphamide (PTCy) for malignant disorders.

**Design/Methods:** We performed a retrospective analysis in children up to 18 years with haematological malignancies who had undergone haploidentical HSCT with PTCy from January 2014 to December 2018.

**Results:** Of the 30 children included, the diagnosis was ALL in 50%, AML in 36%, relapsed Hodgkins lymphoma 7%, MPAL 3.5%, CML in blast crisis 3.5%. HSCT was performed in CR1 in 33%, CR2 in 63%. Minimal residual disease (MRD) negative status was seen in 73%. MRD positivity and sibling donor were found to be statistically significantly associated with risk of relapse (P values 0.042 and 0.007 respectively). Children with ALL received Fludarabine/TBI 12Gy (73%), those with AML received Fludarabine/Melphalan (72%). Peripheral blood stem cells were used in 93%, 80% donors were the father. The mean CD34 infused was  $5 \times 10^6/\text{kilogram}$  with  $6.4 \pm 1.81$  in the children who are alive and  $4.7 \pm 1.01$  in those who died and the difference is statistically significant (P value 0.010). Neutrophil engraftment by D + 21 was documented in 93% of the children. The most important strategy for immunomodulation was early withdrawal of immunosuppression by D+30 if there is no evidence of graft versus host disease (GvHD). Donor lymphocyte infusions using whole blood in graded doses starting at  $1 \times 10^4/\text{kilogram}$  were given pre-emptively in 55% children by day 60 if donor chimerism was less than 99% with no evidence of GvHD. Judicious use of Lenalidomide, Dasatinib, Nivolumab, Ruxolitinib helped reduce the incidence of relapse over a median follow up of 21 months to 14% in this cohort of high-risk children.

**Conclusions:** Pre-HSCT MRD negative status and post-transplant immunomodulation are powerful tools in providing a relapse-free survival of 86% in children with malignant disorders undergoing Haplo SCT with PTCy.

**Keywords:** Haploidentical, HSCT, post-transplant cyclophosphamide, malignant disorders

## HLA-HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH REDUCED-INTENSITY CONDITIONING REGIMEN CONTAINING LOW-DOSE ANTI-THYMOCYTE GLOBULIN (2.5 mg/kg) FOR HIGH-RISK HEMATOLOGICAL MALIGNANCIES

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**Background:** HLA-haploidentical hematopoietic stem cell transplantation (Haplo-HSCT) has been increasingly performed in patients with high-risk hematological malignancies, as well as in patients lacking matched sibling donor. However, the optimal treatment method for Haplo-HSCT has not been established.

**Method:** To evaluate the efficacy and safety of Haplo-HSCT, we retrospectively analyzed patients who received Haplo-HSCT for high-risk hematological malignancies mainly consisting of relapse after allogeneic HSCT in our institute between 2013 March and 2018 December. Conditioning regimen consisted of ATG (2.5mg/kg), MEL (140mg/m<sup>2</sup>), FLU (180mg/m<sup>2</sup>), TBI (3Gy), and Ara-C (0-8g/m<sup>2</sup>).

**Results:** Nineteen patients (AML=12, ALL=4, MDS=1, CML=1, NHL=1, median age=49yrs) were analyzed. Eighteen patients (95%) received Haplo-HSCT for hematologic malignancies relapsed after allogeneic HSCT. Six patients (32%) were in complete remission (CR) at the time of transplant. Eighteen of nineteen patients received peripheral blood stem cell (PBSC), the other received bone marrow (BM). Median follow-up duration was 9 (1-73) months. All patients achieved neutrophil engraftment (median day=10 days). Acute (grade II-IV) and chronic (extensive) GVHD was observed in 3 (16%) patients and 3 (16%) patients, respectively. Overall survival (OS) at 1-y (2-y) was 45% (28%). Nine patients (47%) died of disease relapse and one patient (5%) died of GVHD (acute). No patients died of infection, though two patients (11%) developed post-transplantation lymphoproliferative disorder (PTLD). Among six patients who underwent Haplo-HSCT in CR, with a median follow up of 50.6 (4-73) months, OS at 1-y (2-y) was 80% (80%).

**Conclusion:** Although our study included small number of patients, this study suggested that the Haplo-HSCT for high-risk hematological malignancy is safe and may have efficacy, especially in CR state.

**Keywords:** Allogeneic hematopoietic stem cell transplantation, haploidentical, high-risk hematologic malignancy

## IS HAPLOIDENTICAL HCST SAFE AND EFFECTIVE FOR CHILDREN WITH HIGH RISK ACUTE LEUKEMIA?

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**Purpose or Background:** Hematopoietic stem cell transplantation is the only curative treatment for children with relapse or high risk acute leukemia. Haploidentical HSCT is suitable option when lacking matched related or unrelated donors. In this study we aimed to compare outcomes of HSCT in acute leukemia according to donor type.

**Method or Case:** we reported 65 pediatric patients with acute leukemia who underwent HSCT in Children's Medical Center, Tehran from 2016 to 2019. Based on matching between donor-recipient, patients divided in 3 groups: full match, one locus mismatch and haplo-identical considered as group A, B and C, respectively. All patients received same myeloablative conditioning regimen consist of Busulfan, Cyclophosphamide  $\pm$  rabbit ATG. GvHD prophylaxis was based on Cyclosporine and Methotrexate in group A and B, and post-transplant Cyclophosphamide combined with Cyclosporine A in group C.

**Results or Progress:** 65 Patients (43 ALL, 22 AML) with median age 8.8 years (2-16) were enrolled. Forty-two patients were boys. Group A, B and C consist of 48, 10 and 7 patients. Except two, all patients attained full Chimerism. Two patients in group C who experienced primary graft failure underwent second successfully haplo-HSCT. Acute GvHD developed in 16.7, 10 and 28.5% of cases in group A, B and C, while chronic GVHD happened 4, 10 and 14% in same mentioned groups. With the median follow-up time 12 months (3-19 months), Leukemia free survival (LFS) and overall survival (OS) were 85% and 87.5 % in group A. Moreover, in group B LFS and OS were 70% and 80% as well. However, in group C all patients were alive with complete remission.

**Conclusion or Discussion:** The incidence of GvHD and graft failure was higher in haplo group but relapse risk was lower compared to other groups. Haplo-HSCT represents an alternative choice for children with relapse and high risk acute leukemia.

**Keywords:** Hematopoietic stem cell transplantation, Acute leukemia, Children, Haploidentical, Donor type

## MANAGEMENT OF RELAPSED MYELOYDYSPLASTIC SYNDROME AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Background:** With advances in the treatment-related toxicities of allogeneic hematopoietic stem cell transplantation (allo-HCT) by optimizing conditioning regimens, HLA matching techniques, and post-transplant complication management, relapse remains a major cause of treatment failure after allo-HCT in myelodysplastic syndrome (MDS). We retrospectively analyzed consecutive patients experiencing post-transplant relapse to view the clinical courses, treatment outcomes, and their survival.

**Method:** Relapse type was classified by modifying the definitions in previous reports (Biol Blood Marrow Transplant 2015;21:653). In total, 121 cases were enrolled for hematologic relapse (HmR, n = 83, 68.6%) and molecular relapse (n = 38, 31.4%), which included 18 cases with cytogenetic (CyR) and 20 with imminent relapse (ImR). The response to treatment and survival outcomes were analyzed after categorizing the treatment options as follows: (1) supportive care, (2) early immunosuppressant withdrawal  $\pm$  donor lymphocyte infusion (DLI), (3) cytoreductive therapy alone (hypomethylating agent or intensive chemotherapy), and (4) cytoreductive therapy with additional immunotherapy (DLI or second allo-HSCT).

**Results:** The overall survival rate (OS) rate was 27.3% and OS differed significantly according to the relapse type (HmR 15.3% vs. CyR 50.4% vs. ImR 63.0%,  $p < 0.001$ ), relapse period ( $\geq 6$  mo. 37.9% vs.  $< 6$  mo. 16.6%,  $p < 0.001$ ), and disease at relapse (MDS 36.0% vs. 2nd AML 12.3%,  $p = 0.0012$ ). In the early relapse group ( $< 6$  mo.), all HmR patients expired no matter the form of treatment (Figure A). However, CyR and ImR patients showed an acceptable OS of 40% and 50% following hypomethylating agent with or without immunotherapy. In the late relapse group ( $> 6$  mo.), OS were 28.8%, 57.1%, and 75.0% in the HmR, CyR, and ImR groups respectively, which was significantly different (Figure B,  $p < 0.001$ ). Among the late relapse with HmR group, the cytoreductive therapy with additional immunotherapy showed a favorable OS of 47.6%. In both ImR and CyR patients, early immunosuppressant withdrawal  $\pm$  DLI presented with the best OS of 83.3%.

**Discussion:** In conclusion, CyR and ImR showed better OS than those with HmR, which suggests that the early detection of CyR or ImR before progression to HmR is crucial for improving treatment response and survival outcomes. Further prospective studies will be required to confirm optimal treatment options in this



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challenging patient population.

**Keywords:** Myelodysplastic syndrome, secondary acute myeloid leukemia, hematologic relapse, molecular relapse, Immunotherapy, allogeneic HCT

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## PORCINE ANTILYMPHOCYTE GLOBULIN AS A PART OF CONDITIONING REGIMEN FOR ALLOGENEIC STEM CELL TRANSPLANTATION IN SEVERE APLASTIC ANEMIA

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**Purpose or Background:** Severe aplastic anemia (SAA) is a potential life-threatening bone marrow failure syndrome characterized by pancytopenia and bone marrow hypoplasia. Antithymocyte globulin (ATG) is the drug of choice for immunosuppressive therapy (IST) as well as a part of conditioning regimen for allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients with SAA. In 2004, porcine-ALG(p-ALG) was approved in China to treat SAA, and many investigations showed that p-ALG had satisfactory effect and safety in IST in SAA patients. But p-ALG as a part of conditioning regimen for allo-HSCT in SAA was seldom reported.

**Method or Case:** This study aimed to evaluate the efficacy and safety profile of p-ALG as a part of conditioning regimen for allo-HSCT in patients with SAA. Clinical information of 41 SAA patients receiving allo-HSCT and treated with p-ALG as a part of conditioning regimen was collected and retrospectively analyzed for overall survival rate, early mortality, side effects, and other complications.

**Results or Progress:** All patients engrafted. No fatal side effect during conditioning was observed, and no patient died during conditioning. The 5-year overall survival (OS) rates was  $91.7\% \pm 4.7\%$ . 2 patients developed III-IV aGVHD, and 4 cases with moderate-severe cGVHD were observed.

**Conclusion or Discussion:** In conclusion, p-ALG showed satisfactory effect and safety as a part of conditioning regimen in allo-HSCT for SAA patients. P-ALG could be a potential alternative preparation with lower cost in SAA allo-HSCT.

**Keywords:** Severe aplastic anemia, allo-HSCT, porcine-ALG

## PRETRANSPLANT IMMUNOSUPPRESSIVE THERAPY MAY PLAY A ROLE IN REDUCING GRAFT REJECTION IN HEMATOPOIETIC STEM CELL TRANSPLANTS (HSCT) : RESULTS FROM A MULTI-SPECIALITY CENTRE IN INDIA

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**Background:** HSCT in multiply transfused patients carries a high risk of graft rejection. The use of a pre-transplant chemotherapeutic regimen has been used to ensure durable graft function at other centres. We report our experience from a newly established HSCT centre in Mumbai.

**Method:** Inj. Cyclophosphamide 500 mg/m<sup>2</sup> x Day 1, Fludarabine 30 mg/m<sup>2</sup> x 3 days and Dexamethasone 20 mg/m<sup>2</sup> x 5 days was given thrice, 15 days apart prior to transplant. Data was collected prospectively.

**Results:** 7 patients received the chemotherapy: 5 haploidentical transplants (1 TCR alpha beta depleted and 4 T-cell replete), 1 matched related and 1 matched sibling donor transplant. The children had Wiskott Aldrich syndrome (2), Thalassemia major (1), Pure red cell aplasia (1), metachromatic leukodystrophy (1), Osteopetrosis (1) and Chronic Granulomatous disease (1). The mean age was 5 years (range 9 months - 7 yr 8 months). PBSC was the graft source in all. Donor specific antibodies were positive in 1 patient and needed therapy. Mean cell dose given was 7.8 million CD34+ cells /kg (range 6.5-20 million/kg). 6 patients engrafted. Median time for neutrophil recovery was 14 days (range 9-25). Median follow up of the patients is 55 days (Range 31 - 273 days). There was no mortality. One patient had E. coli sepsis and Posterior reversible encephalopathy syndrome needing intensive care after the 2nd immunosuppressive therapy; all others tolerated the chemotherapy well without any neutropenia or sepsis. Chimerism on Day 28 was >96% in all cases except 1. 3 patients have crossed Day 100 and continue to have chimerism >96%.

**Conclusion:** Though the numbers are small; our success rate is 86%. Thus, pre-transplant immunosuppressive therapy may play a role in preventing graft rejection. As the centre is new, our follow up period is short at present.

**Keywords:** Pretransplant chemotherapy, Engraftment, mortality, post transplant chimerism

## T CELL REPLETE HAPLO HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH POST TRANSPLANT CYCLOPHOSPHAMIDE FOR HEMOGLOBINOPATHIES

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**Introduction:** Hematopoietic stem cell transplantation (HSCT) from an HLA-MRD or MUD remains the only curative therapy for hemoglobinopathies. Only 25% of patients have an HLA matched donor and the prohibitive cost of MUD makes it unaffordable in developing countries. Haploidentical related donors are readily available as an alternate source of stem cells.

**Methods:** This is a retrospective study of haplo-HSCT in 34 consecutive patients with hemoglobinopathies that underwent 36 haplo-HSCT between September 2014 and April 2019. Sixteen transplants were done for TM and 18 for SCD with median age of 7 years (1-26). Donor type: Parents 29; siblings: 7. Graft source: BM 5; PBSC 31. Conditioning regimen: Flu/Bu/Thymo: 24, Thymo/Thiotepa/Flu/Cy/TBI: 10, Flu/Cy/TBI: 2. Median CD34+ dose was  $10.7 \times 10^6/\text{kg}$  (1.67-20.4).

**Results:** Out of 36 transplants; 34 achieved primary engraftment. Median neutrophil and platelet engraftment was on 14 days (12-24) and 17 days (11-35) respectively. Two patients underwent second transplant for graft failure. The incidence of graft failure was 22%. The incidence of grades 2 to 4 acute graft-versus-host disease (GVHD) was 25%, chronic GVHD was 19%. Other complications: CMV reactivation 36%, hemorrhagic cystitis 14% and PRES 19.4%. The 100 day mortality was 20.5 % with sepsis as predominant cause of death in 71% followed by GvHD in 29%. At a median follow-up period of 699 days (range, 26-1628 days); the overall survival (OS) and disease-free survival (DFS) were 85 % and 58%, respectively.

**Conclusion:** T cell replete haploidentical stem cell transplant is a feasible option in patients with no available HLA matched donor. Long term follow up is required for better understanding of the outcome of these patients.

**Keywords:** Haplo HSCT, Hemoglobinopathies, T cell Replete

## THE CLINICAL CHARACTERISTICS OF MONITORING DIFFERENT IMMUNOCYTE SUBSETS CHIMERIC RATE AFTER REDUCED-INTENSITY CONDITIONING RELATED HLA-HAPLOIDENTICAL PERIPHERAL BLOOD HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Purpose or Background:** To investigate the clinical significance of monitoring the chimeric rate of different immune cell subsets after our unique reduced-intensity conditioning related HLA-haploidentical peripheral blood hematopoietic stem cell transplantation (RIC-RH-PBSCT).

**Method or Cases:** 27 patients underwent RIC-RH-PBSCT in our center from July 2013 to 2019 enrolled in this study. All subjects signed informed consent. The chimeric rate of recipients after transplantation was monitored, and the clinical significance of the monitoring of chimeric rate after transplantation was discussed.

**Results or Progress:** 1. 6 patients engrafted to successful neutrophil reconstruction, 8 patients engrafted to successful platelet reconstruction, and 25 patients engrafted to hematopoietic reconstruction at +28d; at +14d, Monitoring of immune cell chimerism revealed that 18 patients achieved complete chimerism, 9 patients had mixed chimerism, 21 patients achieved complete chimerism, 6 patients had mixed chimerism; 2. 16 patients suffered from aGVHD, somatic cells, T cells and NK cells got fully chimeric state in patients with aGVHD at +28d, the chimeric rate of somatic cells, T cells and NK cells in the patients without aGVHD showed mixed chimerism at +28d; 3. Six patients relapsed, the median recurrence time was +3 months; T cells showed mixed chimerism at +14d in relapsed patients, and patients without relapse showed full chimerism at +14d (P=0.034).

**Conclusion or Discussion:** 1. The implantation status can be judged early by monitoring the chimeric rate of immune cell subsets at +14d; if the immune cell subpopulation is not fully chimeric at +28d, it may indicate poor implantation. 2. Monitoring the immune cell subsets after RIC-RH-PBSCT could predict the occurrence of aGVHD. A fully chimeric state of somatic, T-cell, and NK cells at +28 days may be more likely to occur aGVHD. 3. After RIC-RH-PBSCT, the relapse rate of the primary disease was lower at the +14 days when the T cell chimerism reached the fully chimeric state than the mixed chimerism rate.

**Keywords:** Hematopoietic stem cell transplantation, Chimerism, Immunity, Cellular, Graft vs host disease

## THE FIRST AUTOLOGOUS STEM CELL TRANSPLANTATION FOR ACUTE MYELOID LEUKEMIA IN MONGOLIA: A CASE REPORT

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**Background:** More than half newly diagnosed acute myeloid leukemia (AML) will attain a complete remission (CR) with chemotherapy. Yet, without additional cytotoxic therapy, practically all of these patients will relapse. In contrast, patients who receive post-remission therapy may expect higher survival rates. There are three options for post-remission therapy: consolidation chemotherapy, autologous hematopoietic stem cell transplantation (auto-HSCT), or allogeneic HSCT.

Mongolia has introduced auto-HSCT for the first time in 2014. At present, a total of 16 patients have been successfully administered auto-HSCT. In 2019, we initiated the 1st triumphant auto-HSCT for the patient with AML.

**Case:** A 22-year-old man, moderate symptoms had occurred and home-treated in December 2017. From that period of time, he complained of fatigue and exhaustion. June 2018, presented to the hospital with 48% of blast cells with Auer rods in peripheral blood (PB) and 60% bone marrow blast cells with MPO ++, diagnosed AML-M2.

One-time induction therapy following with consolidation treatment were administered, with the high dose cytosine for four courses. In May 2019, patient received auto-HSCT. 10mg/kg CSF was administered for 7 days prior to the collection of PB stem cells. Total of  $2.45 \times 10^6$  / kg ( $0.24 + 0.8 + 1.4$ ) CD34+ cells are collected using an apheresis machine after being mobilized from the bone marrow to PB.

**Progress:** Conditioning regimen protocol had been done by By/Cy/E. CSF was administered 5 mg/kg for 12 days after the stem cell infusion. On the 15th day, the ANC>500 and IRP>5.0, the bone marrow was recovered. Transfusion and additional medication were administered according to the patient's needs. Currently, the patient has been discharged and under the weekly monitoring.

**Discussion:** Auto-HSCT could be an alternative consolidation treatment for AML. Moreover, there might occur relapses after auto-HSCT, but the countries which are not able to perform allo-HSCT, auto-HSCT would be the better option for extending the lifespan.

**Keywords:** Acute myeloid leukemia, autologous transplantation, hematopoietic stem cell, bone marrow examination

## THE IMPACT OF CD34+ AND CD3+ CELL DOSE IN THE GRAFT ON THE INCIDENCE OF GVHD IN CHILDREN RECEIVING ALLOGENEIC HSCT FROM UNRELATED DONOR

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Ho Joon Im<sup>1</sup>, Young-Uk Cho<sup>2</sup>, Seongsoo Jang<sup>2</sup>, Chan-Jeoung Park<sup>2</sup>, Jong Jin Seo<sup>1</sup>

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**Purpose or Background:** Although the graft composition is associated with GVHD, inconsistent results have been reported regarding the optimal dose of CD3+ and CD34+ cells on the incidence of GVHD. The purpose of this study is to evaluate the impact of CD3+ and CD34+ cells dose in the graft on the incidence of acute(aGVHD) and chronic GVHD(cGVHD) in children receiving PBSCT from HLA-matched or 1-allele mismatched unrelated donors (URD).

**Method or Case:** 105 pediatric patients with hematologic malignancy (n=70) or nonmalignant disease (n=35) received PBSCT from matched (8 of 8, n=80) or 1-allele mismatched (7 of 8, n=25) URD at Asan Medical Center Children's Hospital between January 2008 and April 2018. We analyzed the cumulative incidence (CI) of aGVHD and extensive cGVHD according to the dose of CD34+ and CD3+ cells in the graft as well as other parameters including their disease, conditioning regimen  $\pm$  ATG, and HLA disparity.

**Results or Progress:** Of a total of 105 transplants, the median number of infused CD34+ and CD3+ cells were  $9.76 \times 10^6/\text{kg}$  (range, 2.86-34.4) and  $3.95 \times 10^8/\text{kg}$  (range, 0.95-13.51), respectively. The CIs of aGVHD  $\geq$  grade 2 and  $\geq$  grade 3 were 52% and 25%, respectively. Infused CD34+ cells greater than  $13 \times 10^6/\text{kg}$  was associated with higher incidence of aGVHD  $\geq$  grade 3 (40% vs 21%,  $P=0.047$ ). The CD3+ cells more than  $4.8 \times 10^8/\text{kg}$  had an increased incidence of aGVHD grade III-IV (39% vs. 21%,  $P = 0.037$ ). Type of disease, conditioning regimen, the use of ATG and HLA disparity were not associated with the incidence of aGVHD. Of the 102 evaluable patients, the CI of extensive cGVHD was 28%. The CI of extensive cGVHD was significantly lower in 62 patients receiving ATG as a component of conditioning regimen compared to 40 with no ATG (16% versus 47%,  $P=0.002$ ). However, the numbers of CD34+ or CD3+ cells, disease type, conditioning regimen and HLA disparity were not associated with the extensive cGVHD.

**Conclusion or Discussion:** Considering high incidence of aGVHD with  $> 13 \times 10^6/\text{kg}$  CD34+ or  $> 4.8 \times 10^8/\text{kg}$  CD3+ cells in the graft, the dose adjustment of those cells may help in reducing severe acute GVHD after allogeneic URD-HSCT.

**Keywords:** Graft versus host disease, CD34+ cells, CD3+ cells, Unrelated donor, Allogeneic hematopoietic cell transplantation, Children

## HEMATOPOIETIC STEM CELL TRANSPLANT ACTIVITY IN 2018 AND AN UPDATE OF THE PROGRESS IN SRI LANKA

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**Purpose or Background:** HSCT commenced in 2014 at Asiri Central hospital(ACH). Three more centres started HSCTs thereafter. Three are in private hospitals. First National HSCT centre was established at National Cancer Institute, Sri Lanka(NCISL) and commissioned in 2016. This was due to a collaboration between the NCISL and National Blood Transfusion Service(NBTS) with St.Vincent's hospital, Sydney, Australia. This saw infrastructure development, mentorship, training and developing protocols culminating in the first successful autologous HSCT in December 2016. This report documents HSCT activity in 2018 and an update of the progress in Sri Lanka.

### Results or Progress:

#### ACH

5 autologous: 4 myeloma, 1 AL amyloidosis. Age range: 50 to 64 years. Mobilization: G-CSF +/- plerixafor. Conditioning: Melphalan(HDM). No transplant related mortality (TRM). 9 allogeneic: Eight thalassaemia major(TM), 1 severe aplastic anaemia(SAA):matched sibling donor(MSD). For TM;5 matched related donor(MRD), 3 matched unrelated donor(MUD). Conditioning: MRD =ATG-busulfan-cyclophosphamide, MUD=thiotepa-treosulfan-fludarabine-ATG, MSD=fludarabine-cyclophosphamide-ATG. Stem cell source: Marrow= MRD/MSD, PBSC= MUD. All 9 engrafted, achieved full donor chimerism(FDC). 1/9 (MRD for TM) succumbed to GVHD. 8/9 remain transfusion independent. 1/9 (MUD for TM) developed PRCA post HSCT. No response to steroids, plasma exchange, rituximab. Responded to bortezomib.

#### NCISL

50 autologous from 06.12.2016 to 31.01.2019 (30 since 01.01.2018): 45 myeloma, 03 Hodgkin, 01 DLBCL, 01 POEMS. Age range:15-62 years. Male:female=34/16. Cell dose: 2.0-7.2 x10<sup>6</sup>/kg CD34+(mean 4.24). Neutrophil engraftment: Day+ 11-20. TRM:1/50. Mobilization: cyclophosphamide+G-CSF for myeloma & POEMS, salvage chemotherapy followed by G-CSF for HD & DLBCL. Conditioning: HDM for MM/POEMS, BEAM for HD/DLBCL.

Tissue typing and establishment of a donor registry is in progress by NBTS. Allogeneic HSCT planned for late 2019 at National HSCT.



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**Conclusion or Discussion:** 35 autologous (mainly myeloma) and 9 allogeneic [6 MRD & 3 MUD, (mainly thalassaemia)] performed in Sri Lanka in 2018. Plans for allogeneic HSCT at the National HSCT centre are underway

**Keywords:** HEMATOPOIETIC STEM CELL TRANSPLANT ACTIVITY, HSCT, Sri Lanka

## BLINATUMOMAB FOR MINIMAL RESIDUAL DISEASE (MRD) IN ADULTS WITH B CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA (BCP-ALL): MEDIAN OVERALL SURVIVAL (OS) NOT REACHED AT 5 YEARS FOR COMPLETE MRD RESPONDERS

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**Background:** MRD is the strongest predictor of relapse in BCP-ALL. Blinatumomab is a bispecific immunotherapy that redirects T-cells to kill CD19+ target cells. In a single-arm study (BLAST;NCT01207388) in adults with BCP-ALL and MRD, we previously reported 78% (88/113) of patients achieved a complete MRD response after cycle 1 of blinatumomab. Patient incidences of grade 3/4 adverse events, including neurologic events (13%) or cytokine release syndrome (2%), were consistent with previous blinatumomab studies. This report describes the analysis of OS for adults with BCP-ALL and MRD in the BLAST study, with a minimum patient follow-up of 5 years after blinatumomab.

**Methods:** BLAST study enrolled adults with BCP-ALL in first (CR1) or subsequent (CR2+) hematologic complete remission after  $\geq 3$  intensive chemotherapy blocks, with MRD ( $\geq 10^{-3}$ ) at least 2 weeks after the last chemotherapy. All patients received blinatumomab (15  $\mu\text{g}/\text{m}^2$  per day up to 4 cycles). Each cycle was 4-weeks of continuous infusion and 2-weeks off. Complete MRD response was defined as no target amplification, with a minimum sensitivity of  $10^{-4}$ . After MRD response assessment (end of cycle 1), patients could undergo allogeneic hematopoietic-stem-cell-transplantation (HSCT) at any time. Kaplan-Meier estimates of OS were determined after long-term follow-up (5 years). A conditional landmark of 45 days (the end of cycle 1) was used for subgroup analyses by complete MRD response.

**Results:** Of 116 patients with MRD who received blinatumomab, OS was evaluated for 110 patients with Philadelphia chromosome-negative (Ph-) BCP-ALL and <5% blasts at enrollment, including 74 who received HSCT in continuous complete remission (CCR) after blinatumomab. With a median follow-up of 59.8 months, median OS was 36.5 months (95%CI:22.0-not estimable [NE]). Table 1 At 5-year outcomes with vs without

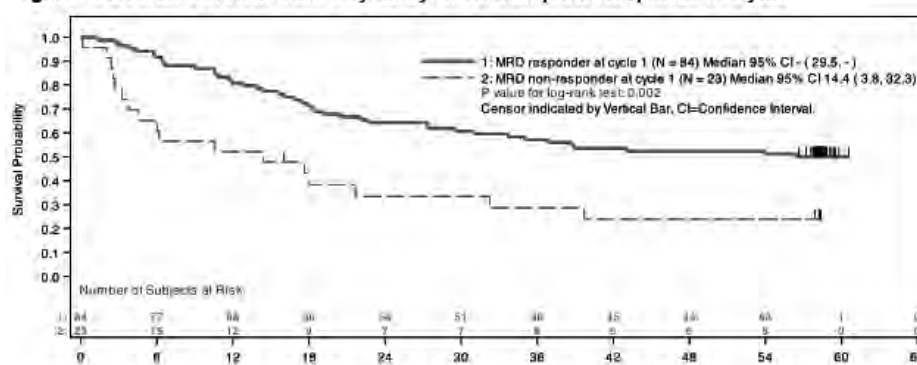
Table 1.		
	With HSCT	Without HSCT
Alive in CCR	40.5%	19.4%;
Relapse	23.0%	72.2%;
Death without relapse	36.5	8.3%.

#### HSCT in CCR.

Analyses of OS by complete MRD response in cycle 1 (n=107) excluded patients with no central MRD assay (n=1) or inadequate MRD test sensitivity (n=2). Median OS was not reached (95%CI:29.5 months-NE) for complete MRD responders (n=84) and 14.4 months (95%CI:3.8-32.3) for MRD nonresponders (n=23;log-rank p=0.002;Figure1). Estimated 5-year survival was 43% overall (95% CI: 34%-52%) and 50% for complete MRD responders (95%CI:39%-60%). Among HSCT recipients in CCR, median OS from HSCT was not reached (95%CI: 25.7 months-NE) for complete MRD responders (n=61) and 16.5 months (95%CI:1.1-NE) for MRD nonresponders (n=10;log-rank p=0.065). Among patients with MRD in CR1, median OS was not reached (95%CI:29.5 months-NE) for complete MRD responders (n=60) and 10.6 months (95%CI:2.7-39.7) for MRD nonresponders (n=13;p=0.008).

**Summary/Conclusions:** In the 5-year follow-up analysis of a multinational study of adults with BCP-ALL in hematologic complete remission with MRD, median OS was 36.5 months after blinatumomab. Median OS was not reached among patients with a complete MRD response in cycle 1 of blinatumomab. These results provide support for long-term OS benefits associated with blinatumomab treatment in adults with BCP-ALL and MRD.

**Figure 1. Overall Survival from Day 45 by MRD Complete Response in Cycle**



PE-183

# HEALTH-RELATED QUALITY OF LIFE (HRQOL) OF BLINATUMOMAB VERSUS STANDARD OF CARE CHEMOTHERAPY (SOC) IN PATIENTS WITH RELAPSED OR REFRACTORY(R/R) PHILADELPHIA CHROMOSOME-NEGATIVE B-CELL PRECURSOR (Ph- BCP) ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN A RANDOMIZED, OPEN-LABEL PHASE 3 STUDY (TOWER): A SUBGROUP ANALYSIS BY PRIOR ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (ALLOHSCT)

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**Background:** TOWER study showed patients with r/r Ph- BCP ALL who received blinatumomab had longer overall survival and improved HRQoL versus patients who received SOC. Because ALL patients who relapse from previous HSCT have poorer prognosis, we analyzed HRQoL of TOWER patients with/without prior alloHSCT.

**Methods:** Adults(n=405) with r/r Ph- BCP ALL were randomized 2:1 to 2 cycles of induction blinatumomab (n=271) or SOC(n=134), followed by up to 3 consolidation cycles; 12 months of maintenance was allowed. AlloHSCT was allowed after cycle 1. HRQoL was assessed in cycle 1 (days 8,15,29) using EORTC QLQ-C30 Questionnaire. For global health status and functioning scales: higher score indicates better HRQoL; symptom scales/items: lower score indicates better HRQoL. Time to deterioration analyses assessed the treatment effect based on a 10-point deterioration (clinically significant threshold) from baseline.

**Results:** Of 342 evaluable patients (blinatumomab,n=247;SOC,n=95); 114(blinatumomab ,n=85;SOC,n=29) and 228(blinatumomab,n=162;SOC,n=66) did and did not, respectively, have prior alloHSCT. In those with no prior alloHSCT, changes in global health status were minimal for blinatumomab and SOC(Figure 1). In contrast, patients with prior alloHSCT, global health status modestly improved in the blinatumomab group but worsened by ≥10 points at all time points for SOC, indicating clinically meaningful deterioration. Changes in functioning scales were minimal in blinatumomab arm, both with/without prior alloHSCT, except for relatively improved emotional scores in patients with prior alloHSCT. In contrast, SOC patients had worsening in most functioning scales, regardless of prior alloHSCT status. This effect was most marked in those with prior alloHSCT, physical, role, and social functioning deteriorated by ≥10 points). Similar patterns were observed for

symptom scales/items:blinatumomab was associated with improved or less worsening in symptom scores versus SOC, most symptom scores worsened in the SOC arm, especially patients with prior alloHSCT, for whom all symptoms (except dyspnea) deteriorated by  $\geq 10$  points. Compared with SOC, blinatumomab was associated with a delayed time to clinically meaningful deterioration, particularly patents with prior alloHSCT(Figure 2).

**Conclusions:** In patients with r/r Ph- BCP ALL, blinatumomab was associated with improved HRQoL vs SOC, regardless of whether patients had received prior alloHSCT. Notably, however, the HRQoL benefit of blinatumomab was most pronounced among patients with prior alloHSCT

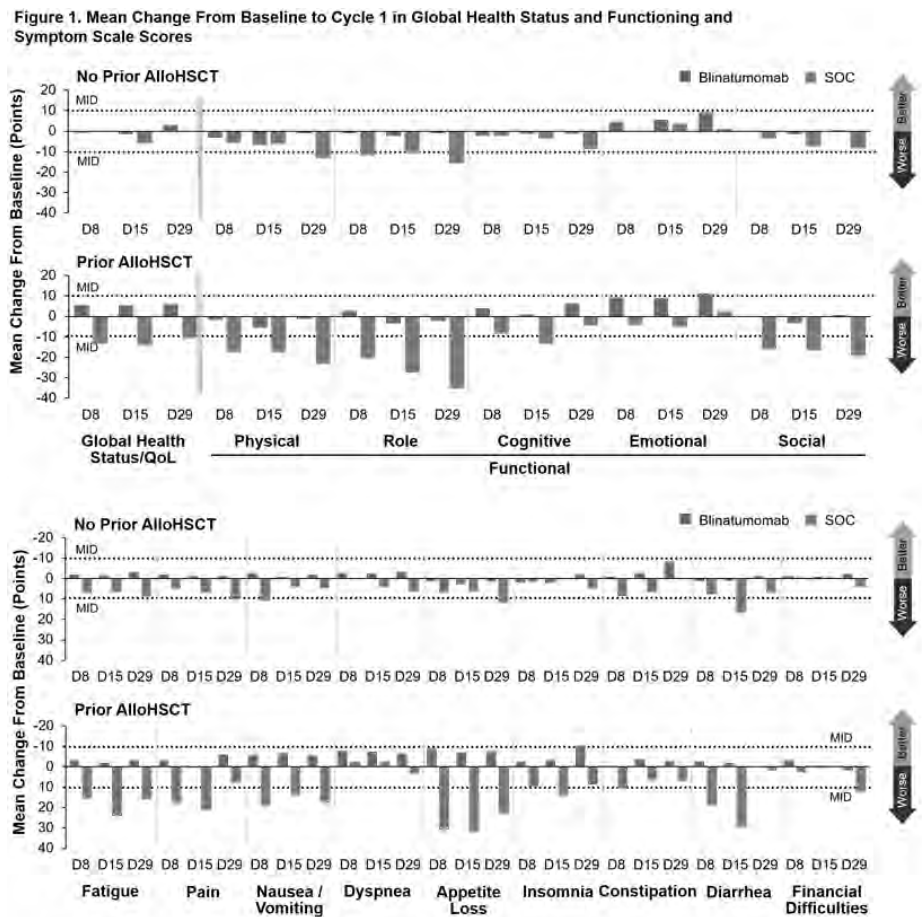
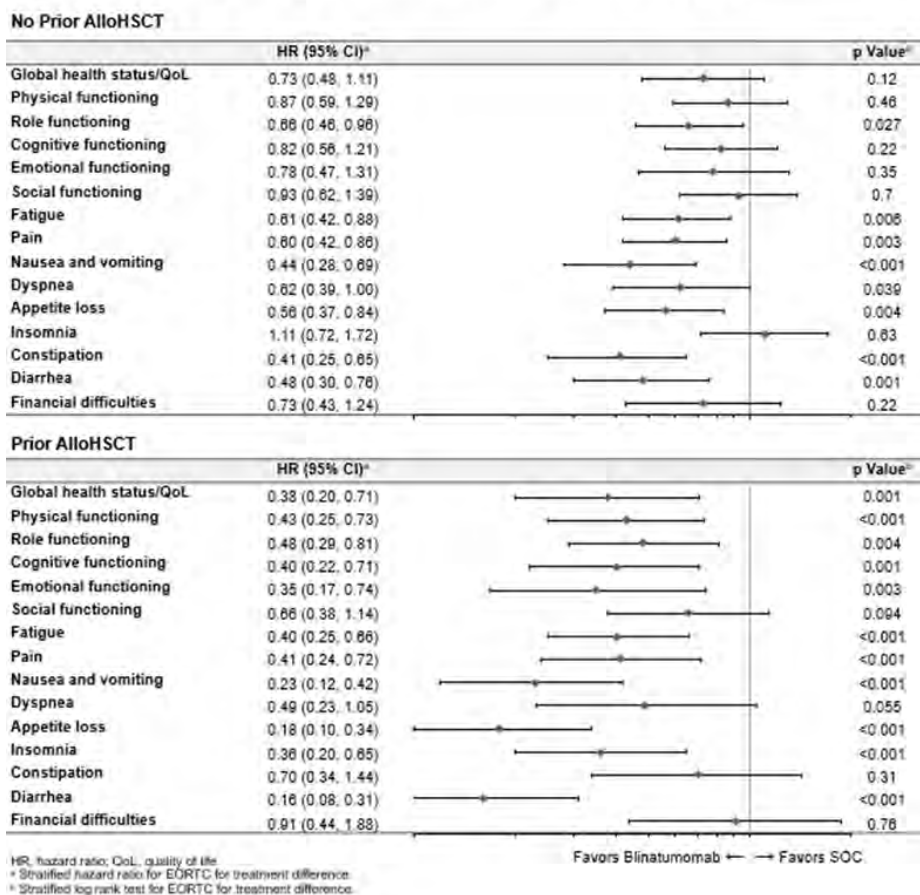


Figure 2. Time to Clinically Meaningful Deterioration in HRQoL of Blinatumomab vs SOC



## FIVE HUNDRED CASES OF HAEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) AT A MALAYSIAN PRIVATE MEDICAL CENTER

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**Introduction:** The first case of bone marrow transplant in Malaysia was performed on a child at University Hospital (UH) in 1987. Six years later, the procedure was performed on an adult in UH. This review studies the first 500 cases of HSCT done at SJMC which was the first private medical centre to perform HCST in Malaysia.

**Methodology:** This was a retrospective study of 500 adult patients who underwent HSCT in Subang Jaya Medical Centre (SJMC) from 1999 and 2018. The HSCT patient records were reviewed. The biodata of the patients, the indications for HSCT, the type HSCT and source to stem cells were studied. The engraftment period and treatment outcome were reviewed.

**Results:** Autologous HSCT was done in 340 patents and represented 68% of all HSCT activity, whereas Allogeneic HSCT was performed in 160 patients represented 32% of all HSCT including 25(5%) Mini-allogeneic and 5(1%) Haploidentical transplantation.

The age range for autologous HSCT recipients was 12 years old to 72 years old (mean age 45.42), which was wider compared to the narrower range of allogeneic HSCT recipients of 14 years old to 66 years old (mean age: 35.95).

The male to female ratio was 3:2 for both autologous and allogeneic HSCT.

The majority (99%) of all transplant recipients received peripheral blood as a source of stem cells. For autologous HSCT recipients, 336 received peripheral blood as HSCT source and 5 received from a combination of peripheral blood plus bone marrow. For allogeneic HSCT, a total of 157 patients received peripheral blood, 1 received from bone marrow and 1 received from combination of bone marrow and peripheral blood.

**Keywords:** HSCT, SJMC

## 1,2,3,4,6-PENTA-O-GALLOYL-BETA-D-GLUCOPYRANOSIDE SUPPRESSES MYC EXPRESSION AND INHIBITS MULTIPLE MYELOMA CELLS PROLIFERATION

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**Background:** Multiple myeloma (MM), is the second most common hematological malignancy. Despite the available treatment options, MM remains an incurable disease and the treatment outcome for patients has not been satisfactory. Therefore, the discovery of novel agents greatly boosts the potential therapeutics for MM. The natural compound 1,2,3,4,6-Penta-O-galloyl-beta-D-glucopyranoside (PGG) has been shown to exhibit antitumor activities against various cancer cells. Therefore, in this study we evaluated the antitumor effect of PGG on MM cell lines.

**Results:** PGG treatment inhibited the growth of three tested MM cell lines in a dose- and time-dependent manner. Cell cycle analysis revealed that PGG treatment caused cell cycle arrest in G1 phase. Annexin V positive cells, Caspase 3/7 activity, and protein expression level of cleaved caspase 3 was significantly increased by PGG treatment suggested that PGG induced apoptosis in MM cell. MYC hyperactivation was observed in more than half of MM patients. MYC inhibition leads to MM cell death, hence MYC is an attractive target for MM treatment. PGG decreased the protein and mRNA levels of MYC and reversed the mRNA expression of MYC target genes p21, p27 and cyclin D2. In addition, PGG treatment inhibited protein expression of DEPTOR which commonly overexpressed and have therapeutic potential in MM. Conversely, PGG antagonized the cytotoxic effect of bortezomib in combination treatment. However, PGG showed synergistic anti-myeloma effect with another proteasome inhibitor MG132. Moreover, MYC inhibitor JQ1 synergizes bortezomib effect against MM.

**Conclusion:** These findings also provide a valuable information for the combination treatment of proteasome inhibitors with the particular type of chemicals for patients with MM. Altogether, our results demonstrated anti-myeloma effect of PGG and supported further development of this compound for the treatment of MM.

**Keywords:** multiple myeloma, MYC, DEPTOR, G1 arrest, apoptosis, proteasome-inhibitors



## **CURRENT STATUS OF BLOOD AND MARROW TRANSPLANTATION IN KOREA**

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Korean Blood and Marrow Transplantation Nursing Society was founded in 1998 and has been collected the data of the status of BMT in Korea.

It was performed 33,885 cases of transplantation from 1983 to 2018.

It showed the percentage of BMT for adult was 78.6% and for pediatrics 21.4%.

Regarding the distribution of diagnosis, AML was 8,702 cases (25.7%), NHL 5,314 (16.9%), ALL 4,436 (13.1%) and MDS was 1,952 cases (5.8%).

Depending on the types of BMT, Autologous transplants were 14,590 (43.1%) cases, Sibling Allogeneic 9,372 (27.7%), Unrelated 6,625 (19.6%), Haplo Mismatched 2,501 (7.4%) and Cord Blood transplants were 797 (2.4%) cases.

Peripheral Blood was used in 27,173 cases (80.2%), Bone Marrow 5,588 (16.5%), and Cord blood was used in 792 cases (2.3%).

In 2018, 42 of 46 institutions performed 2,664 cases of transplantation.

Male was 58.6% (1,560 cases) and female was 41.4% (1,104 cases). Depending on the distribution of diagnosis, AML was 685 cases (26.2%), ALL 287 (11.6%), MM 465 (18.0%), and CML was 4 cases (0.8%).

Regarding the types of BMT, Autologous transplantation was 1135 cases (42.6%), Unrelated 511(19.2%), Matched sibling Allogeneic 510(19.1%), Haplo mismatched 468 cases (17.6%) and Cord Blood transplantation was 40 cases (1.5%). The number of Familial mismatched BMT has been increasing but matched sibling Allogeneic BMT was decreased.

2,587 cases (97.1%) of Peripheral Blood transplant was performed, the number of it has been increasing.